A NOTE ON NON-INFERIORITY MARGINS

RE: CRITICALLY APPRAISING NONINFERIORITY RANDOMIZED CONTROLLED TRIALS: A PRIMER FOR EMERGENCY PHYSICIANS

To the editor: Tobacco has been clearly associated with a variety of illnesses. Therefore, we may state that the excessive use of tobacco is inappropriate. Physicians might, therefore, wish to counsel their patients to use only appropriate amounts of tobacco. But there is the rub; how much is appropriate? Clearly, the answer is none. One cigarette is one too many. This flies in the face of the old adage, "everything in moderation." When something is amply demonstrated to be harmful, then it should not be used. Ever. Not even once. With this in mind, we must be somewhat critical of Al Deeb, Azad, and Barbic,[1] who ask whether the non-inferiority margins used are generally appropriate in non-inferiority trials. The tobacco analogy goes only so far, of course, because just about everybody agrees that tobacco is harmful, whereas (almost) nobody is actively clamoring to have non-inferiority margins abolished. So, clearly, there is a difference in perception. But is there a commensurate difference in substance? We think not.

Al Deeb, Azad, and Barbic[1] also asked whether the new treatment has tangible benefits over the standard treatment. Presumably, the answer, in general, would be yes, at least in expectation before the trial. If so, then this forms the basis of a superiority trial aimed at establishing this superiority.[2] This superiority must then be weighed and balanced against any compensating inferiority. When presented with the option to purchase one of two widgets, a better but more expensive one or an inferior but less expensive one, the paradigm is *not* to first establish that the costs are within an acceptable margin and then on that basis to go with the better one as long as it is statistically significantly better. Likewise, the paradigm is not to first establish that the qualities are within an acceptable margin and then on that basis go with the cheaper one as long as it is statistically significantly cheaper. Educated consumers do not sweep one of the two considerations under the carpet and then free themselves to consider only the other one; they consider *both*, simultaneously. This is how it has to be. The need to do so is no less when these decisions are rendered not by patients themselves but rather by researchers acting on behalf of the patients who form their constituency. One treatment is generally more effective, but it also carries a larger risk of side effects. The new treatment is almost as effective but carries a smaller risk of side effects. Does it belong on the market? Possibly, but the non-inferiority margin plays no role (or should play no role) in this determination.

A more compelling role of the non-inferiority margin may be in comparing the two treatments (as opposed to only asking whether the new one should be on the market). But even here, as already discussed, a proper cost/benefit analysis is warranted. All things considered, which treatment is more appropriate? This is a question that, in general, cannot be answered in a vacuum, because each patient brings to the table his or her own set of value judgments.[3] Some may be willing to tolerate more side effects for greater efficacy; others may not be. This is for the patient to decide, or, at the very least, for the physician to decide *responsibly*, on behalf of the patient. Even if we consider just one patient, it is still true that using a non-inferiority margin to eliminate one component of the comparison may be expedient, and may be what is best for the decision maker who wants to simplify his or her decision-making process; however, it certainly is not in the best interest of the patient, who is served best by an informed cost/benefit analysis.

Complicating the matter is the precedent for using non-inferiority margins when the new treatment is suspected of being inferior to the existing one on the basis of the primary efficacy end point. But leeches were once precedent too, and the suggestion that surgeons wash hands between operations also met with resistance at one time. These examples should provide a clear lesson that precedent can never be taken as an adequate replacement for acting responsibly, especially in a medical setting. If non-inferiority margins are not helping the system, then they

© Canadian Association of Emergency Physicians
CJEM 2015;17(3):237-238 DOI 10.1017/cem.2015.40

https://doi.org/10.1017/cem.2015.40 Published online by Cambridge University Press

should not be used. Alas, they are not helping the system. Hence, they should not be used.

Vance W. Berger, PhD

National Cancer Institute, Rockville, MD; University of Maryland, Baltimore County, Baltimore, MD

REFERENCES

1. Al Deeb M, Azad A, Barbic D. Critically appraising noninferiority randomized controlled trials: a primer for emergency physicians. *CJEM* 2015;17(3):231-6.
2. Durkalski V, Berger VW. Reformulating non-inferiority trials as superiority trials. *Biom J* 2009;51(1): 185-92.
3. Berger VW. On the generation and ownership of alpha in medical studies. *Control Clin Trials* 2004;25(6): 613-9.

https://doi.org/10.1017/cem.2015.40 Published online by Cambridge University Press