RE: A NOTE ON NON-INFERIORITY MARGINS

To the editor: We read with interest the letter by Berger[1] in which non-inferiority (NI) trials were criticized, and the author advocated for the elimination of NI margins and effectively substituting NI trials with superiority trials and/or superiority trials with unique methodologies, like information-preserving composite end points.[2] We need to highlight that our paper was not intended to discuss which study design methods are more appropriate when comparing two treatments or the advantages and disadvantages of each strategy. Our paper was intended to provide a logical framework on how to critically appraise existing NI trials and NI trials to come.[3] We perceived a possible misconception in the way that NI margins were addressed in the letter by Berger and would like to address that. Ideally, an NI margin should represent the most allowable inferiority that has *no clinical* significance even though it might have a statistically significant inferiority. This primarily involves clinical judgment, as well as sound statistical methods. To illustrate this in a hypothetical example, consider comparing ibuprofen to acetaminophen in their effects at reducing pain, using a visual analogue scale for quantification of pain. If we want to test that acetaminophen is non-inferior to ibuprofen, how can the NI margin be set in such a study? If it has been shown in one study that a minimum of a 3-mm difference in the visual analogue scale reaches clinical significance, then anything smaller than this difference would be deemed not clinically significant. As a result, one can set the NI margin at 3 mm on the basis that a reduction of at least 3 mm would represent a clinically significant reduction of pain. A result showing anything less than 3 mm, even if statistically significant, does not represent a clinically important effect, thus establishing non-inferiority. However, if we are testing an outcome such as mortality, then one could argue that even the smallest non-inferiority margin might not be acceptable, as even an absolute difference of 1%, for example, with the new treatment being inferior, would be decided to be clinically important. This provides the rationale to introduce a *clinically* non-inferior drug (even if statistically inferior) given it has other tangible benefits. Nevertheless, because NI margins involve clinical judgment that can be subjective, it is certainly conceivable and worrisome that NI margins might be misused in allowing a clinically inferior drug to be introduced in the market. This is why clinicians need to execute clinical judgment when interpreting NI margins.

Although beyond the scope of our paper and our discussion, we would like to comment on Berger's suggestion on substituting NI trials with superiority trials using composite end points or information-preserving composite end points methodology.[2] While this is ideal and ambitious, we suspect it might not be realistic due to feasibility issues in trial design, sample size, and cost. We therefore feel it is still appropriate to have non-inferiority designs as a means to continue further research and progress.

At the end of the letter, Berger wrote:

> "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."

We agree with Berger on this, but this is not an argument against NI trials. In fact, NI trials, if conducted appropriately, might provide further options for both the patient and the physician. It is definitely important to tailor specific treatments to specific patients. Adding a new non-inferior treatment to clinical care does not necessarily eliminate the use of the previously established treatment.

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