The Superiority of Patient Engagement and Shared Decision-Making in Noninferiority Trials

Richard M. Hoffman, MD, MPH[1] *and Mary McNaughton-Collins, MD, MPH*[2]

[1]Medicine Service, New Mexico VA Health Care System, Albuquerque, NM, USA; [2]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA.

J Gen Intern Med 29(1):16–7
DOI: 10.1007/s11606-013-2593-z

The Users' Guides to the Medical Literature has been a bible to many general internists seeking to develop skills in critically appraising the medical literature and delivering evidence-based care. However, the most recently published guide on how to use a noninferiority trial struck a discordant note.[1] The topic was timely, given the recent spate of noninferiority articles being published in the literature—a PubMed search of "noninferiority" and "clinical trials" identified 126 citations in 2012. Clinicians accustomed to reading studies to determine whether a new treatment is more effective than a standard treatment or placebo in preventing morbid events or death have found the concept of noninferiority to be perplexing. The rationale for conducting noninferiority studies is that a new treatment would be valued if it were not much worse than a standard treatment in preventing adverse clinical outcomes, and was also safer, more convenient, or cheaper. The guide provided a helpful framework for understanding and interpreting these studies, but fell short in addressing applicability.

The article began by identifying issues related to unwarranted conclusions of noninferiority, including whether investigators could have biased results in favor of the novel intervention by comparing it with suboptimal standard treatment, whether event rates observed with standard treatment exceeded those seen in historical trials, and whether investigators used both an intention-to-treat analysis and the more conservative estimate generated by a per-protocol analysis. However, the key issue is setting the noninferiority threshold—determining the differences in clinical effectiveness outcomes such that the new treatment could be considered noninferior as opposed to inferior. In other words, how much worse can the new treatment be for clinicians and patients to still consider it acceptable.

While the authors present some useful statistical criteria for setting the noninferiority limit, they acknowledge that there is no gold standard method and no expectation that the investigators' selected limit will be clinically acceptable to physicians or patients. The authors encourage readers to use "your own judgment rather than accepting that of the investigators" and "act as an advocate for your patients by assessing whether they are likely to consider the advantages of the novel treatment worth the potential loss in effectiveness." The authors further advise readers to rely on their clinical experience and "what you consider to be the values and preferences of most of your patients." They even suggest that clinician readers "may choose not to offer the novel treatment to patients" if the upper boundary of the confidence interval for the primary outcome exceeds the reader's noninferiority threshold.

We agree that interpreting noninferiority trials is difficult, and appreciate the authors' cautious approach to applying results from such studies. However, we are concerned by the suggestion that physicians should attempt to judge the values and preferences of their patients, which could lead to not offering a novel treatment. Unfortunately, physicians are notoriously inaccurate in assessing patients' values,[2] and making unilateral decisions undermines patient autonomy. We suggest that a more useful strategy would be to engage patients in shared decision-making (SDM).[3] Clinicians can explain, or provide a decision support tool that describes the clinical issue, the nature of the decision, the alternatives, and the potential benefits and harms of the alternatives. These tools should convey tradeoffs between less burden and less effectiveness, using plain language and graphics to better support patient decision-making, even among those with low health literacy. Patients could be encouraged to identify the outcomes that are most important to them and helped to make a decision that is concordant with these values.

A 2012 perspective in the New England Journal of Medicine by Oshima Lee and Emanuel highlighted the value of SDM, particularly through using patient decision aids.[4] The authors cited a Cochrane Collaborative review of 86 randomized trials that showed that receiving decision aids increased knowledge and realistic perceptions of outcomes, increased involvement in decision making, and improved values-based choice.[5] Furthermore, the authors pointed out that wider adoption of SDM could potentially reduce health care costs, because informed patients facing preference-sensitive decisions are more likely to opt for conservative therapies. The Affordable Care Act (ACA) explicitly encourages greater use of shared decision-making

Published online August 24, 2013

in health care. However, the authors noted that little had been done to further this goal in the 2 years following the enactment of ACA. Oshima Lee and Emanuel called on the Centers for Medicare and Medicaid Services to begin certifying and implementing patient decision aids with the goal of promoting shared decision-making, improving the quality of medical decisions, and reducing costs. Physicians and patients trying to apply results from noninferiority trials could certainly benefit from such efforts, though we are not aware of any decision aids that have been developed within this context.

In addition to encouraging clinicians to elicit patients' perspectives, values, and preferences about findings from published noninferiority trials, we also advocate for more proximal patient involvement. We encourage investigators to seek patient input before deciding on their noninferiority threshold to enhance patient centeredness and to reduce burdening clinicians with having to "use [their] own judgment" about the published threshold. The Patient Centered Outcomes Research Institute (PCORI) recently published a draft statement from their methodology committee that, suggests as a standard for patient centeredness and engagement, that research proposals "[e]ngage patient informants, persons representative of the population of interest, in all phases of patient-centered research."[6]

While making decisions based on results from noninferiority trials explicitly accounts for the tradeoffs between benefits and harms, such preference sensitive decisions, though often unrecognized, are actually quite common in medicine—whether in the setting of cancer screening, starting or stopping medications, or undergoing elective surgeries. The evidence base for these decisions might be inconclusive, there could be important tradeoffs between benefits and harms, or recommendations might be inconsistent or controversial—ideally requiring patients to determine their values for the various potential outcomes and to make an informed decision. The expectation that health care providers support their patients in making such challenging decisions is at the heart of patient-centered care.

Acknowledgements: *Drs. Hoffman and McNaughton-Collins report receiving partial salary support as Medical Editors for the Informed Medical Decisions Foundation, a not-for-profit 501(c)(3) private foundation that develops content for patient education programs and has an arrangement to produce these programs with a for-profit company, Health Dialog. No other potential conflicts of interest are relevant to this article.*

The authors thank Dr. Michael Barry for his helpful comments on an earlier draft of this manuscript.

Corresponding Author: *Richard M. Hoffman, MD, MPH; Medicine Service, New Mexico VA Health Care System, 1501 San Pedro Dr SE, Albuquerque, NM 87108, USA (e-mail: rhoffman@unm.edu).*

REFERENCES

1. **Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH.** How to use a noninferiority trial: users' guides to the medical literature. JAMA. 2012;308(24):2605–2611.
2. **Mulley AG, Trimble C, Elwyn G.** Stop the silent misdiagnosis: patients' preferences matter. BMJ. 2012;345:e6572.
3. **Charles C, Gafni A, Whelan T.** Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med. 1997;44(5):681–692.
4. **Oshima Lee E, Emanuel EJ.** Shared decision making to improve care and reduce costs. N Engl J Med. 2013;368(1):6–8.
5. **Stacey D, Bennett CL, Barry MJ, et al.** Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2011;10:CD001431.
6. **Helfand M, Berg A, Frum D, Gabriel S, Normand S-L.** Public comment draft report of the Patient-Centered Outcomes Research Institute (PCORI) Methodology Committee presented on July 23, 2012, and revised thereafter. Patient Cent Outcomes Res Inst. 2012.