Critical Appraisal of Non-Inferiority Randomized Controlled Trials

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Non-inferiority (NI) randomized controlled trials (RCTs) are becoming increasingly popular types of clinical trials, particularly in cardiovascular, infectious disease, and oncology research. In this issue of the Journal, the Evidence-Based Practice Review Section includes our first critical appraisal of a NI trial. A brief primer on NI trials is included below to complement the critical appraisal. We base our NI trial appraisal on the concepts in the JAMA Users' Guide to the Medical Literature: How to use a Noninferiority Trial.[1] Further details can be found in this Users' Guide reference.

The purpose of traditional RCTs is to determine whether a new therapy is superior to a placebo or an active control. However, NI trials are different, in that their purpose is to examine whether a new therapy is non-inferior or "not that much worse" than the comparison. The new therapy in a NI trial should offer some type of advantage, such as, decreased toxicity or greater convenience, relative to the standard therapy.

Most NI trials have an objective to examine an efficacy outcome. With this objective, the comparison arm should be an active control that is the gold standard therapy for the condition being treated. However, more recently, NI trials have also been designed with the objective of assessing whether a new therapy is "not that much more harmful", and these have typically evaluated cardiovascular harms compared to a placebo control.

Three key pointers to critically appraise a NI trial differently than a traditional superiority RCT include examining whether the study has been designed to ensure that:

1. The target population, comparison arm, and outcomes measured are chosen optimally, rather than chosen to find a minimal difference between the new therapy and the comparison (that is, biased towards a NI conclusion);

2. The analysis is conducted as both intention to treat (which is biased towards a NI conclusion) and per protocol (a biased analysis in general, but less likely to falsely conclude NI), with minimal difference in results between both types of analyses; and

3. The NI margin (how much worse the new therapy can be) is clinically reasonable, and does not allow excessive harm, or excessive loss of benefit with the new therapy. Often statistically derived NI margins are too large to be clinically reasonable to clinicians and patients.

We hope these pointers will help readers become comfortable with critically appraising and using NI trials in their practice.

About the Section Editor

Cynthia Jackevicius, BScPhm, PharmD, MSc, BCPS-AQ Cardiology, FCSHP, FAHA, FCCP, FCCS a Professor of Pharmacy Practice at Western University of Health Sciences, is the Evidence-Based Practice Section Editor. Dr. Jackevicius teaches evidence-based practice skills to health care professionals. She advocates for the adoption of an evidence-based practice, incorporating the best available evidence, patients' values and preferences, and clinicians' expertise into clinical decision-making.

References

1. Mulla SM, Scott IA, Jackevicius CA, You JJ, Guyatt GH. Users' Guide to the Medical Literature: How to use a non-inferiority trial. JAMA 2012;308:2605-11. doi: 10.1001/2012.jama.11235.