Reply to Phillips, Morris, and Walker

We thank the authors for their thoughtful comments [1]. DOOR/RADAR (Desirability of Outcome Ranking/Response Adjusted for Duration of Antibiotic Risk) [2] is a new paradigm and thorough evaluation of the methodology is helpful to better understand its strengths and limitations in different settings.

We agree that DOOR novelty can increase complexity. It will require experience and understanding before it is as natural and familiar as common effect measures. Improved understanding of clinical relevance to reduce the arbitrary nature of the alternative hypothesis can be aided by links to common metrics in traditional settings, for example, differences in means although these are often equally arbitrary.

DOOR/RADAR evaluates treatment *strategies*. RADAR rankings are based on the treatment received (not assigned). The design doesn't guarantee better ranks for a specific treatment conditional upon similar clinical outcomes. ITT is intact.

As with other composite outcomes, DOOR/RADAR results don't necessarily imply similar results on component outcomes. This is concerning when component outcomes have differing levels of importance and the influence of the less important components is too large. This can apply to RADAR given composition of both clinical and antibiotic use outcomes. Other versions of DOOR (ie, ranking based only on the ordinal table of clinical outcomes without consideration of antibiotic use) reduce this concern. One premise of RADAR is that less antibiotic use has distinct patient and societal benefits (reducing future resistance). RADAR may be inappropriate for tuberculosis trials for these reasons. DOOR based solely on the ordinal table of clinical outcomes may be a reasonable option in tuberculosis.

DOOR is only one piece of information to be considered when interpreting overall trial results and deciding how to treat future patients. Component outcomes should be evaluated using confidence intervals to elucidate potential concerning effects. DOOR/RADAR could indicate superiority even with small between-arm differences in an important component outcome (although noninferiority [NI] trials also allow for small differences in outcomes). When utilizing RADAR, sensitivity analyses (eg, evaluation of DOOR based only on the ordinal table) are prudent.

Although DOOR may transform some NI trials, DOOR and NI may be viewed as complementary. Thorough DOOR analyses require component outcomes analyses (some potentially of a NI nature), whereas the utility and pragmatism of NI trials can be strengthened with DOOR analyses assessing global outcome to inform clinical decision-making.

When designing studies using DOOR, researchers evaluate whether sufficient information regarding component outcomes is obtained from the trial to aid clinical decision-making in the context of prior beliefs about the components and given the relative importance of component outcomes. This challenge is similar to other composite endpoints, for example, MACE in cardiovascular trials or progression-free-survival in oncology trials, where teams decide whether to size the study on the composite, specific component outcomes (eg, death), or a compromise.

We share concern for manipulation as with other composites. DOOR/RADAR shouldn't be used to hide inferiority of important component outcomes. Appropriate construction of the DOOR requires careful infection-specific evaluation. During trial design, simulation studies varying assumptions regarding effects on the components helps to vet appropriate application and increase method transparency.

Notes

Financial support. V. G. F. has received institutional grant support through the National Institutes of Health (UM1-AI104681; K24-AI093969).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2016;62(6):815–6
 DOI: 10.1093/cid/civ1003