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DOOR/RADAR: A gateway into the unknown?

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Dear Editor

We read with interest the recent DOOR/RADAR proposal to transform non-inferiority into superiority trials[1]. We agree with the authors that non-inferiority trials are complex to conduct, often have large, impractical sample sizes and are prone to biases and manipulation compared to superiority trials.

Antimicrobial resistance is perhaps the greatest challenge facing healthcare today[2]. We therefore welcome their laudable attempt to consider radical and pragmatic alternatives to non-inferiority trials. We are concerned, however, that DOOR/RADAR suffers from several flaws and may therefore not represent a viable alternative to non-inferiority trials.

Firstly, a clinical interpretation for the proposed treatment effect of 'the probability of a better DOOR for a randomly selected participant from the new *vs.* the old strategy' is far from clear. The authors arbitrarily propose 60% for the alternative hypothesis for sample size calculations. Introducing a completely new effect measure may increase rather than reduce complexity, and could potentially be misinterpreted.

Secondly, despite the superiority framework, intention-to-treat analyses do not retain their standard interpretation since, providing patients experience good outcomes, the intervention will always be ranked higher than the control regardless of treatment actually received.

Thirdly, combining clinical outcome and treatment duration into a single variable, obscures important differences in the clinical outcome. DOOR/RADAR will show superiority even if there is an imbalance between arms in an important clinical outcome (say death) provided it occurs in a relatively small proportion of patients and the more favourable outcomes are reasonably well balanced between arms.

To illustrate, we applied DOOR/RADAR to the recently completed non-inferiority trials RIFAQUIN[3] and REMoxTB[4], where three different 4-month regimens were shown not to be non-inferior to the 6-month control regimen using a pre-specified 6% non-inferiority margin. There was strong evidence ($p<0.0001$) that each 4-month regimen had a higher DOOR than the standard 6-month regimen (Table) using either a 4-category or 7-category clinical outcome, with treatment effects of 0.66-0.68 and 0.62-0.64 respectively. This is not unsurprising given that >50% of patients had the most successful outcome on each arm (favourable clinical outcome with no grade 3/4 adverse events) and therefore the DOOR is driven by the shorter treatment duration in the 4-month arms *by design* rather than the poorer outcomes on the 4-month regimens. It is hard to see what this adds to the standard non-inferiority analysis of the trials given that there has been unanimous consensus that none of these regimens are viable alternatives to the standard 6-month regimen.

Power in DOOR/RADAR is maximised with a clinical outcome with fewer categories, or where most patients fall into a small number of categories, as illustrated by the higher treatment effects and z-scores with the 4-category than the 7-category outcome in our example. Thus DOOR/RADAR can be manipulated by careful choice of the clinical outcome to increase the chance of superiority.

The SCOUT-CAP trial has been designed based on DOOR/RADAR; our results suggest that considerable further evaluation of this approach is urgently needed to avoid an inconclusive result with no impact on clinical practice.

Table. Application of the DOOR/RADAR approach to the shorter duration 4-month regimens from the REMoxTB and RIFAQUIN trials. The 4-category and 7-category clinical outcomes are based on a composite of the primary efficacy and safety endpoints from the trials. Patients excluded from the primary analyses based on pre-randomisation data were also excluded in this analysis (modified intention-to-treat).

	4-category clinical outcome: 1. Favourable with no grade 3 or 4 adverse events; 2. Favourable with at least one grade 3 or 4 adverse event; 3. Not assessable; 4. Unfavourable.		**7-category clinical outcome**: 1. Favourable (culture negative at end of follow-up) with no grade 3 or 4 adverse events; 2. Favourable (REMoxTB: no negative culture at end of follow-up, RIFAQUIN: follow-up curtailed <18m by protocol amendment) with no grade 3 or 4 adverse events; 3. Favourable with at least one grade 3 or 4 adverse event; 4. Not assessable; 5. Unfavourable (not relapse or treatment failure); 6. Unfavourable (relapse or treatment failure without culture confirmation); 7. Unfavourable (culture confirmed relapse or treatment failure).	
Treatment arm (compared to standard 6-month regimen)	Probability of a better DOOR for a randomly selected participant from the new strategy (95% CI)*	Test that new strategy has a higher DOOR**	Probability of a better DOOR for a randomly selected participant from the new strategy (95% CI)*	Test that new strategy has a higher DOOR**
REMoxTB: Moxifloxacin and ethambutol regimen	0.68 (0.64, 0.72)	$p < 0.0001$ ($z = 10.7$)	0.62 (0.59, 0.65)	$p < 0.0001$ ($z = 7.4$)
REMoxTB: Moxifloxacin and isoniazid regimen	0.68 (0.65, 0.72)	$p < 0.0001$ ($z = 10.8$)	0.64 (0.60, 0.67)	$p < 0.0001$ ($z = 8.2$)
RIFAQUIN: Moxifloxacin and rifapentine	0.66 (0.60, 0.71)	$p < 0.0001$ ($z = 6.0$)	0.62 (0.56, 0.67)	$p < 0.0001$ ($z = 4.4$)

* 95% bootstrap percentile confidence intervals. ** Wilcoxon rank-sum test.

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