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Risk-based Heterogeneity of Treatment Effect in Trials and Implications for Surveillance of Clinical Effectiveness Using Regression Discontinuity Designs

To the Editor:

The Perspective by Iwashyna and colleagues highlights the importance of stratifying clinical trial participants by level of risk to assess effect heterogeneity (1). By comparing efficacy across values of a risk score, an “efficacy threshold” can be identified at which patients could be provided (or not provided) the intervention. A critical question, however, is how to assess the real-world effectiveness of an efficacy threshold identified in such a trial. The quasiexperimental regression discontinuity offers an approach to evaluate real-world effectiveness of interventions found efficacious in subgroups of trial participants. Regression discontinuity analysis leverages situations in which interventions are instituted at a threshold of a continuously measured variable (2–4). Noise in measurements of that assignment variable quasirandomly assigns patients to be above or below the threshold and thus to intervention or control. An efficacy threshold that was previously identified in a trial designed according to Iwashyna and colleagues’ specifications could be later tested for effectiveness in real-world settings—and across different patient populations and care delivery systems. Investigators could use observational regression discontinuity methods for active surveillance of effectiveness by evaluating changes in the relationship between predicted risk and observed outcomes at the risk threshold for efficacy suggested by a trial. Health care systems may further use regression discontinuity analyses to explore whether risk thresholds identified in clinical

trials optimally identify thresholds of efficacy among their patient populations, allowing titration of optimal risk cutoffs at individual hospitals. We encourage further investigation of methods to pair risk-based analysis for heterogeneity of treatment effects in clinical trials with post-trial, continuous surveillance and optimization of real-world effectiveness through quasiexperimental approaches. ■

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Reply

From the Authors:

We appreciate the letter from Dr. Walkey and Dr. Bor about our article (1). They cleverly suggest ways in which regression discontinuity designs (RDD) may be quite helpful. RDD may be superior to other observational approaches to monitor ongoing implementation of the results of randomized clinical trials (RCTs) that have been analyzed to detect heterogeneity of treatment effect (HTE). This is a potentially useful strategy for organizations willing to commit organizational resources to both a nuanced discussion of RCT results and big data infrastructure to support it. We note, of course, that this can only occur if the original RCT has been reported and analyzed for HTE by baseline risk.

One of the benefits of examination for HTE by baseline risk of death is that it provides data about the net benefits of a treatment. Rather than the RCT providing a single population average estimate, with HTE analyses, we can move toward personalizing estimates of the benefits of a therapy. These data can support the implicit judgments clinicians are constantly called on to make.

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Net benefit thinking recognizes that some patients may benefit very much from a therapy, in which case most such patients should get it. Some patients are much more likely to be harmed than helped, and those patients should not get that therapy. And some patients are in a middle range of modest net benefit, in which case individual preferences and clinician-patient-family conversation are key.

To implement an RDD monitoring strategy, an organization would need to come to a consensus as to where these thresholds should be set after each RCT. In particular, the organization would need to agree on: where are the everyone/some and some/no-one thresholds for our hospital or clinician group? Such a collective conversation in the face of new evidence might be of great value but also requires willingness to standardize practice regarding that therapy.

We note that Dr. Walkey and Dr. Bor suggest new approaches to refining knowledge about HTE *after* the primary observations have been made in RCTs. True randomization remains a gold standard, and we do not believe their letter argues that even sophisticated observational approaches such as RDD could replace the primary role of intentional randomization. We are excited that they have suggested another reason to report and analyze RCTs for HTE by baseline risk. Such HTE reporting and analysis must become an accepted standard to provide the foundation for the work they are developing. ■

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