

The DOOR is Open: A Patient-Centric, Pragmatic Approach to Clinical Trials based on Benefit:risk

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Course Description: Randomized clinical trials are the gold standard for evaluating the benefits and harms of interventions but they often fail to provide the necessary evidence to inform medical decision-making (DeMets and Califf, JAMA 2011, 305:713-714). One primary reason for this is a lack of awareness of the nature of benefit:risk, which is the most important question when treating patients in clinical practice. This is the motivation for using a patient-centric, benefit:risk approach to the design, monitoring, analysis, interpretation and reporting of clinical trials and medical product development.

Standard approaches to benefit:risk evaluation synthesizing information obtained from separate marginal analysis of each outcome do not address the most important questions for clinical practice as they are not patient-centric. They fail to incorporate associations between outcomes and recognize the cumulative nature of outcomes in individual patients, suffer from competing risk complexities in the interpretation of component outcomes, and since efficacy and safety analyses are often conducted on different populations, generalizability to patient populations is unclear. Treatment effect heterogeneity is typically evaluated based on a single efficacy or safety endpoint, and rarely evaluated based on benefit:risk.

These challenges can be addressed by placing increased emphasis on patient-centric benefit:risk evaluation and questions of a pragmatic origin to match their clinical importance. These challenges can be addressed by placing increased emphasis on patient-centric benefit:risk evaluation and questions of a pragmatic origin to match their clinical importance. In this short course, we will discuss the patient-centered method of assessing benefit:risk, called the Desirability of Outcome Ranking (DOOR). The desirability of outcome ranking (DOOR) is a paradigm for the design, analysis, interpretation and reporting of clinical trials and other research studies based on patient-centric benefit:risk evaluation (Evans SR, Rubin D, Follmann D et al. Clin Infect Dis. 2015; 61:800-806, Evans SR, Follmann D. Stat Biopharm Res. 2016;8:386-393). The DOOR methodology uses outcomes to analyze patients rather than patients to analyze outcomes by comparing the experiences of trial participants in different treatment arms by the desirability of the overall patient outcome. The motivation for DOOR is to address the above limitations, increasing pragmatism and addressing the most important “real world” question to aid clinical decision-making: how do resulting patient experiences, when comprehensively considering benefits and harms, compare between therapeutic alternatives?

In this course, we present several ways to define a DOOR outcome, which represents a global patient response constructed on the basis of important clinical outcomes. We describe two complementary statistical approaches for analyzing clinical trial data using the DOOR methodology, with applications to clinical trials in infectious diseases and other disease areas. We present an interactive web-based tool for implementing the DOOR methodology that allows statisticians and clinical researchers to easily perform the analyses. We discuss methods for sizing clinical trials with the DOOR outcome as the primary endpoint. Finally, we briefly discuss further developments in design and analysis of randomized trials using the DOOR methodology, including (1) subgroup analyses, (2) benefit:risk evaluation in longitudinal and

survival trials, (3) integrated benefit:risk analysis of multiple trials, and (4) group-sequential and adaptive designs for monitoring trials.