The Order of Operations is Important:

It is Time to Correct the Clinical Trial Arithmetic

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Typically in clinical trials efficacy and safety are evaluated in silos, one outcome at a time. However this approach: fails to incorporate associations between or the cumulative nature of multiple outcomes in individual patients, suffers from competing risk complexities during interpretation of individual outcomes, fails to recognize important gradations of patient responses, suboptimally evaluates treatment effect heterogeneity based on a single endpoint rather than benefit:risk considerations, and since efficacy and safety analyses are often conducted on different populations, generalizability is unclear. In recognition of this, the Council for International Organizations of Medical Sciences (CIOMS) recently recommended: (1) transitioning benefit-risk evaluation as a post-hoc exercise to incorporating benefit-risk considerations into clinical trial design, and (2) a pragmatic patient-centric approach to benefit-risk assessment to ensure proper evaluation of the benefits and harms as experienced by patients. The desirability of outcome ranking (DOOR) is a paradigm for the design, analysis, and interpretation of clinical trials based on a comprehensive patient-centric benefit-risk evaluation developed to address these limitations and the CIOMS recommendations, and advance clinical trial science. In this paradigm outcomes are used to analyze patients rather than patients being used to analyze outcomes. The experiences of trial participants in different treatment arms are compared by the desirability of the overall patient outcome, 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? The DOOR paradigm, and freely available online tools for design and robust analyses are discussed, and illustrated using examples.

BIO

Dr. Scott Evans is a Professor and Founding Chair of the Department of Biostatistics and Bioinformatics and the Director of The Biostatistics Center at Milken Institute School of Public Health of the George Washington University. He is the: Director of the Statistical and Data Management Center for the Antibacterial Resistance Leadership Group (ARLG) funded by NIAID/NIH; the PI of the Coordinating Center for the Exercise and Nutrition Interventions to Improve Cancer Treatment-Related Outcomes (ENICTO) in Cancer Survivors Consortium funded by the NCI/NIH, and the co-PI of the Data Coordinating Center of the Clamp OR Delay among neonates with Congenital Heart Disease (CORD-CHD) clinical trial funded by the NHLBI/NIH. He is the Co-Chair of the Benefit-Risk Balance for Medicinal Products Working Group of the Council for International Organizations of Medical Sciences (CIOMS); Editor of a mini-Series on DSMBs for the NEJM Evidence; a member of an FDA Advisory Committee; and the President-elect of the Society for Clinical Trials (SCT). He is a recipient of the Mosteller Statistician Award, the Zackin Distinguished Collaborative Statistician Award, the Founders Award from the American Statistical Association (ASA), an elected member of the International Statistical Institute (ISI), and is a Fellow of the ASA, SCT, and the Infectious Disease Society of America (IDSA).