

# Commentary: Statistics in Therapeutic Innovation and Regulatory Decision Making

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It is a pleasure and a privilege to introduce a series of papers that bear witness to the vital roles of the discipline of Statistics in medical product development and therapeutic innovation, regulatory decision making, and hence to health and well-being at both the individual patient and public health levels. The series editors, Drs Olga Marchenko and Alex Dmitrienko, and all authors are to be commended for providing a forward-looking collection of engaging and informative discussions that give readers insight into the statistical thinking of leaders from academia, the biopharmaceutical and medical devices industries, and government.

In his 1999 textbook, Matthews<sup>1</sup> emphasized that the methodology underpinning randomized clinical trials (RCTs) is firmly based in statistical theory, and that the success of RCTs “perhaps constitutes the greatest achievement of statistics in the second half of the twentieth century.” Based on the pioneering work of Ronald Fisher<sup>2,3</sup> and enhanced by other visionaries such as Paul Meier<sup>4</sup> and Austin Bradford Hill,<sup>5</sup> RCT statistical methodology has continued to evolve,<sup>6</sup> and this series of papers captures this evolution very well. While attention initially focused on fixed-design superiority trials, contemporary statisticians have expanded the field to include additional designs such as adaptive and non-inferiority trials, each of which has become widely used and has contemporaneously driven the development of the regulatory science that goes hand in hand with clinical and statistical sciences to bring new therapies to market. These topics are discussed in this series, along with both frequentist and Bayesian approaches.

Other topics covered include new methods for the analysis of dose-finding trials, methods whose importance is evidenced by the observation that “improper dose selection remains one of the key drivers of the large attrition rates observed in confirmatory studies.”<sup>7</sup> Multipopulation tailoring clinical trials, which efficiently examine treatment effects in specific subpopulations as well as an overall patient population, are increasingly being employed as personalized medicine develops.<sup>8</sup> The latest approaches to the perennial problem of missing data are also addressed.

The series is noteworthy in two other ways. First, it embodies a lifecycle approach to drug development, an important approach that enables rational decision making when moving from one phase of development to another.<sup>9</sup> Discussions of

studies throughout the preapproval continuum are presented. Second, and also extending the first point into the realm of post-marketing surveillance, it embraces statistical methodologies for evaluating drug safety during both development and therapeutic use. It is fair to say that until relatively recently, analytical methods for efficacy data have been more well developed than those for safety data, in large part due to the contrast in the nature of endpoints of interest: therapeutic confirmatory trials typically have just one or two efficacy endpoints, while “safety data are multidimensional and complex.”<sup>10</sup> It is therefore gratifying that the last two papers in the series address this extremely important domain.

As an editorial board member of TIRS, I am pleased to see this collection of papers appear in our journal, which has a long tradition of publishing statistical work. I trust that you will enjoy reading them as much as I have.

—J. Rick Turner, PhD  
Member, TIRS Editorial Board

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