Viewpoint

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The Role of Futility Analyses in Alzheimer's Disease Clinical Trials

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Futility analyses in clinical trials are designed for all the right reasons: we want to stop exposing subjects to unnecessary risk and inconvenience if there is no chance that the intervention will provide them with benefit, and we want to direct resources toward more promising treatments.

However, there is no infallible formula or procedure that generates the needed analysis plan to accomplish these goals. Various methods have been proposed to calculate the probability of a statistically significant final result conditional upon interim data (Bayesian and non-Bayesian approaches to conditional probability); or to define group sequential stopping boundaries (1).

In general, these approaches require that you know in advance what the treatment difference between treated and untreated patients should be and/or that you set arbitrary false-negative and false-positive rates, acknowledging that you may be wrong no matter what you do. These challenges are especially evident in a field like Alzheimer's disease (AD), where there are new mechanisms of action, trial designs, and outcome measures, and where few approved therapies exist to guide answers to these questions. Estimations or guesses to these unanswered questions affect the accuracy as well as the statistical power of the analysis.

The AD field has experienced successful, as well as unsuccessful, futility analyses. We learned from a futility analysis of the SCarlet RoAD trial of low-dose gantenerumab for prodromal AD that the trial was futile, which led to stopping that study as well as the Marguerite RoAD trial of the same low dose in patients with mild AD (2). This enabled us to learn more about the molecule in an open-label extension study, and to subsequently launch a larger, longer, global Phase 3 program, maximizing drug exposure with a five-fold higher dose (3-5). More recently, a futility analysis of the Phase 3 CREAD study of crenezumab allowed us to stop two global trials in early AD, but to continue the Alzheimer's Prevention Initiative trial for delaying the onset or prevention of autosomal dominant AD in people who are PSEN1 E280A mutation carriers (6, 7).

Every futility analysis, like every clinical trial, involves a ratio of potential benefit for the analysis to potential risk for conducting it, with the risk being the possibility of stopping a trial even when the treatment has some degree of benefit, and even when the degree of benefit is of the magnitude that the trial was originally designed to show. We must continue to evolve our futility analysis approaches, just as we continue to evaluate new molecules and trial designs.

Disclosures: R. Doody is a current employee and shareholder of F. Hoffmann-La Roche Ltd, Basel, Switzerland and Genentech, Inc., South San Francisco, CA, USA.

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