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August 23, 2023

Dr. Colin Begg:

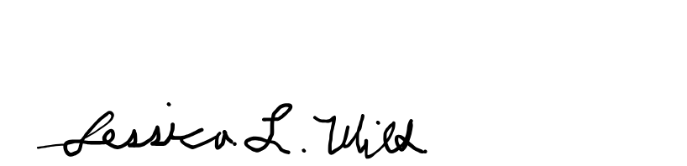
Enclosed is the article, “Uppstrapping to Determine Futility: Predicting Future Outcomes Nonparametrically from Past Data,” submitted for your consideration as a research paper. While the article includes statistical concepts, it is focused on the application of the statistical methods to interim monitoring in the context of clinical trial designs.

Advances in cancer biology and immunology continue to refine our understanding of cancer mechanisms and actionable therapeutic targets, extending treatment options for patients beyond conventional cytotoxic drug regimens. With these advances, novel schemes for cancer classification have been proposed, which transcend traditional criteria based on tissue histology. Basket trials, one type of master protocol, are uniquely suited to the development of biomarker targeted therapies for solid and hematologic malignancies. However, recently developed statistical methods using Bayesian approaches have not been commonly used in practice with potentially inefficient designs, such as Simon’s two-stage design, chosen instead. For example, Bayesian hierarchical models are ideal for basket trials, as they naturally facilitate information sharing across baskets. They are designed to investigate targeted therapies among multiple cancer histologies (or baskets), and attempt to consolidate trials that would otherwise have been conducted for each cancer subtype. These trials are designed with the hypothesis that the molecular feature is a stronger determinant of treatment response than tumor histology, yet acknowledge the possibility of heterogeneous results.

The article first discusses current approaches to interim futility monitoring and their limitations, emphasizing the current need for more flexible nonparametric alternatives. We then introduce the upstrap as one such alternative to traditional methods which avoids any parametric assumptions by relying on repeated resampling of the current interim dataset to make predictions about the probability of trial success. Evidence of the upstrap’s potential performance benefits are presented through simulated trials with interim futility monitoring where upstrapping is directly compared to more traditional group sequential and conditional power based futility monitoring. These simulations illustrate the upstrap’s potential to achieve comparable or even improved performance with traditional methods in terms of expected sample size, statistical power, and type I error rates.

Thank you for your time and consideration of this manuscript. Future correspondence pertaining to this manuscript should be addressed to me by email (jessica.wild@cuanschutz.edu).

Sincerely,



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