Title: Bayesian Adaptive Phase I-II designs for Evaluating Safety and Efficacy in Dual-Agent Oncological Drug Development

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Abstract: Recent changes in U.S. drug and biologics regulations regarding early phase testing in oncology inspired by FDA Project Optimus (https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus) suggest a potential sea change in statistical approach. In the traditional paradigm, Phase 1 testing considers only safety outcomes, and seeks a single *recommended Phase 2 dose* (RP2D), typically the *maximum tolerated dose* (MTD), to advance to Phase II testing of preliminary efficacy. While effective with traditional cytotoxic agents, this approach is inappropriate for more modern cancer therapies (e.g., vaccines), for which the efficacy curve may rise rapidly with dose, and then flatten for doses far below the MTD. As such, Project Optimus suggests a search not for a single R2PD, but rather a *recommended dose range* (RDR), from the lowest minimally effective dose to the highest safe dose. A subset of doses from within the RDR can then be advanced to a fully randomized Phase 2 trial focusing on comparative efficacy. While FDA has recently issued guidance on the matter (FDA, 2023), there is still substantial room for interpretation and appropriate methods development. In this setting, Bayesian statistical methods (Carlin and Louis, 2009) emerge as a helpful strategy, since they are more easily understood by clinical trialists, and facilitate combination of information across multiple data types and sources.

In this talk, we describe a seamless Phase I-II design for testing a new cancer drug, where the sponsor is interested in the drug's value as both a monotherapy, and in combination with a second drug. Phase I begins with a monotherapy "run-in" period, where we seek the RDR while restricting Drug 2's dose to zero. This portion of the design uses a clinical utility index to trade off safety (measured as a binary endpoint) and efficacy (which can again be binary, or a continuous response such as a biomarker change over 6 months). Correlation among the two competing endpoints is captured through copula modelling. We then use Bayesian optimization techniques (Garnett, 2023) to search two-drug dose combinations. Building on Houde et al. (2010), our bivariate dosing model employs a bivariate Gaussian process approximation in order to provide smooth and efficient estimation over the two-dimensional dosing grid. After a sufficient number of 3-patient cohorts have been evaluated, the region of highest posterior utility identifies a two-dimensional recommended dose region, from which the two or three best dose combinations can advance to Phase II. This design includes a futility stop if no combination doses having comparable clinical utility are identified, whereupon doses from the previously identified monotherapy RDR are advanced.

Ideally, Phase II is a randomized comparison of the efficacy of 2-3 promising combination doses, the optimal monotherapy dose, and placebo, with the possibility of dropping unpromising doses and reallocating those patients to doses that remain. Phase I patients on arms selected for Phase II testing will have the opportunity to seamlessly continue on into Phase II, increasing power. We evaluate both stages of our design using simulation, where in Phase I we study the probability of correct dose selection, while in Phase II we return to the traditional benchmarks of Type I error and power. The proposed design appears to satisfy modern regulatory guidelines for Phase I-II oncology trials, while offering improved efficiency, flexibility, and interpretability.

References:

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