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Autore	DOMENICANO, ILARIA
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Sommario	This work summarizes the two years of research that I have conducted at Dana-Farber Cancer Institute(DFCI)/Harvard T.H. Chan School of Public Health, in Boston (MA, USA), where I collaborated with Lorenzo Trippa (Associate Professor at Harvard University and Dana Farber Cancer Institute) and Steffen Ventz (Assistant Professor at University of Rhode Island). The thesis is divided in two main parts. The first part represents the main contribute of my research and on which I spent a dominant portion of my PhD period. In this part, called "Bayesian Uncertainty-Directed Dose Finding Designs", we introduce Bayesian uncertainty directed (BUD) designs for dose finding trials. This class of designs assigns patients to candidate dose levels with the aims of maximizing explicit information metrics at completion of the trial, while also avoiding the treatment of patients with toxic or ineffective dose levels during the trial. Explicit information metrics provide, at completion of the clinical trial, accuracy measures of the final selection of optimal or nearly optimal dose levels. The BUD approach utilizes the decision theoretic framework, and builds on utility functions that rank candidate dose levels. The utility of a dose combines the probabilities of toxicity events and the probability of a positive

response to treatment. We discuss the application of BUD designs in three distinct settings; (i) dose finding studies for single agents, (ii) dose optimization for combination therapies of multiple agents, and (iii) precision medicine studies with biomarker measurements that allow dose optimization at the individual level. The proposed approach and the simulation scenarios used in evaluation of BUD designs are motivated by a Stereotactic Body Radiation Therapy (SBRT) study in lung cancer at Dana Farber Cancer Institute. The second part of the thesis, called "Inference in Adaptive Trials under Time Trends in the Patient Population", is a smaller project that we started only a few months ago, and thus many questions about the topic have not been investigated yet. The project addresses the problem of changes in the patient population over time during a clinical trial. Standard analysis methods in clinical trials implicitly assume that the patient characteristics do not change over time, and the treatment effect remains constant during the study period. Since trials run for many years, this hypothesis may not hold and time trends in the patient population can constitute a potential source of bias in both estimation and testing of the treatment effects. This is especially important for trials using adaptive randomization, where the randomization probabilities change as a function of the outcome observed during the trial. Consider a randomized two-arm trial of total sample size N with a binary endpoint. The response probability for the first N/2 patients is 0.2 for the control arm and 0.5 for the experimental arm. Due to changes in patient population, the response probabilities changes to 0.4 and 0.7 for the remaining patients in the two arms respectively. With balanced randomization (BR), where patients are allocated to the arms with equal probabilities, the expectation of the estimated overall response probabilities are 0.3 and 0.6 for the two arms, and the difference is 0.3, which is constant before and after the change. However, if response adaptive randomization is employed and the randomization probability changes to 2:1 for experimental vs control for the last N/2 patients, the expectation of the estimated overall response probabilities are now (0.2N/4 + 0.4N/6)/(N/4 + N/6) = 0.28 and (0.5N/4 + 0.7N/3)/(N/4 + N/3) = 0.61 for the control and experimental arms with a difference of 0.33, which is inflated by 10%. In this work, we propose a procedure which reduces the bias of treatment effect estimates and preserves the frequentist operating characteristics. We account for time trends by using Generalized Additive Models (GAMs) to estimate the treatment effect. We then use a parametric bootstrap to obtain valid inferences for treatment effects. The testing procedure can be implemented for any adaptive design and any estimator of the treatment effect. We apply our procedure to some well-known Response Adaptive Randomization (RAR) designs to evaluate the performance of the proposed method. For each design, we assess the estimation and testing capabilities of the method by simulating different time trends in both standard multi-arm clinical trials and platform trials.

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