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Multistage adaptive biomarker-directed targeted design for randomized clinical trials

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ABSTRACT

Background: Precision medicine is changing how patients are treated and how therapies are developed. In recent years, biomarker-directed targeted designs have been developed for pharmaceutical development aimed at patient subpopulation with a specific disease etiology. To integrate multistage testing into the targeted designs enhances flexibility of targeted trials by enabling sequential monitoring and stochastic curtailment.
Methods and results: We studied a multistage adaptive design for targeted trials with either normally distributed endpoint or binary endpoint. The design is based on the fact that distribution of the sequence of test statistics from multistage testing is asymptotically well approximated by a Brownian motion in targeted trials with normally distributed continuous endpoint or binary endpoint. This study has demonstrated that the targeted multistage design improves study efficiency, information accumulation and conditional power as compared with its untargeted counterpart. Furthermore, our study has indicated that biomarker performance plays a crucial role in efficiency and effectiveness of the multistage adaptive design. The sensitivity and specificity of a biomarker used for patient enrichment influence level of heterogeneity of the targeted study population, and subsequently impact overall trial efficiency and statistical power as well as information accruement and conditional/predictive power for stochastic curtailment. When performance of a biomarker is imperfect, conditional/predictive power at an earlier stage may be over-estimated, resulting invalid early stopping decision. Thus, great care is needed to ensure that biomarker performance is considered in statistical planning of the multistage targeted trials.
Conclusions: In summary, the multistage adaptive design provides targeted trials with flexibility in multistage testing and early stopping while retaining the rigor of the study design.

1. Introduction

Precision medicine is reshaping the landscape of healthcare. A broad patient population sharing similar clinical symptoms may differ in disease etiology and may respond differently to a treatment regimen. It is no longer scientifically, economically, and ethically justifiable to treat a broad patient population with a regimen that only benefits a small portion of the patients. Targeted clinical trial designs use biomarker to identify and enrich patients likely to benefit from a new treatment regimen. In contrast to the conventional clinical trials based on broad eligibility criteria, targeted trial designs are aimed at developing clinical treatment for a subpopulation of patients with specific molecular etiologies. Simon and Maitournam have shown that targeted designs can improve efficiency of a randomized clinical trial [1,2]. Several biomarker-directed targeted trial designs have been developed including biomarker stratified design, biomarker

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strategy design, biomarker enrichment design, and Bayesian adaptive randomization design [3–7].

Central to targeted trial designs is a diagnostic decision rule that is used to select target patient subpopulation with a specific disease etiology that an investigative drug under study is aimed at. A diagnostic decision rule, referred to as a diagnostic test, includes both a single biomarker and a classifier based on multiple biomarkers. The performance of the diagnostic test depends on both false positive and false negative errors. An ideal biomarker with perfect performance would create a homogeneous patient population of a specific disease etiology for clinical testing. However, a real-world biomarker with imperfect performance may cause a study population to become a heterogeneous and unrepresentative, consequently leading to inefficiency and even wrong decision-making. Hence, multistage testing will help monitor deviations of study population in targeted designs.

Sequential monitoring has become an integral part of clinical trial design, enabling investigators to evaluate risk-benefit, data quality and nature of treatment effect for informed decision-making on whether or not to continue the trial [8]. Thus many trials are designed with the provision for multistage test. In recent years, this field has rapidly evolved to a broader area of adaptive design that allows adaption or modification to some aspects of a clinical trial after its initiation without undermining the validity and integrity of the trial [9]. In the area of biomarker-directed targeted designs, adaptive design development includes incorporation of early biomarker discovery and validation into a clinical trial [10–12], decision-making on steering a trial from a broad patient population to a biomarker-defined subpopulation [6], and biomarker-guided adaptive randomization [4].

In this article, we investigate the impact of an imperfect biomarker on a multistage adaptive design for biomarker-directed targeted trial, and on how the information is accrued in alpha spent and conditional power. We first develop a framework for multistage targeted design for randomized clinical trials with normally distributed endpoints or binary endpoint (Section 2 and Appendix A). We then study properties of the multistage design in biomarker-directed targeted trials and the implications of biomarker performance on the multistage designs including information accumulation, alpha spent, trial efficiency, study power, and type-I error (Sections 3 and 5). Furthermore, we examine stochastic curtailment in multistage targeted trials and the impact of biomarker performance on the decision-making (Sections 4 and 6). We conclude with a discussion (Section 7).

2. Multistage adaptive biomarker-directed targeted (MAT) design

In the proposed MAT design illustrated in Fig. 1, the target patient population with a specific disease etiology is identified by a biomarker (positive) and randomized into treatment arms; whereas patients with biomarker negative status in the initial screening are taken off from the study. Biomarker performance plays a central role in patient enrichment process which impacts the composition of the target study population and study result. Multistage testing is planned to sequentially monitor whether ongoing biomarker-directed patient enrichment can achieve primary study objectives. Multistage testing is intended to evaluate (1) whether the treatment benefit in the ongoing biomarker-directed target patient population is comparable with the assumption in the study design which is based on prior studies to derive sample size, and (2) whether the difference between treatment arms in the biomarker-directed patient population exceeds early-stopping thresholds. Thus, MAT combines the advantages of both targeted and adaptive designs.

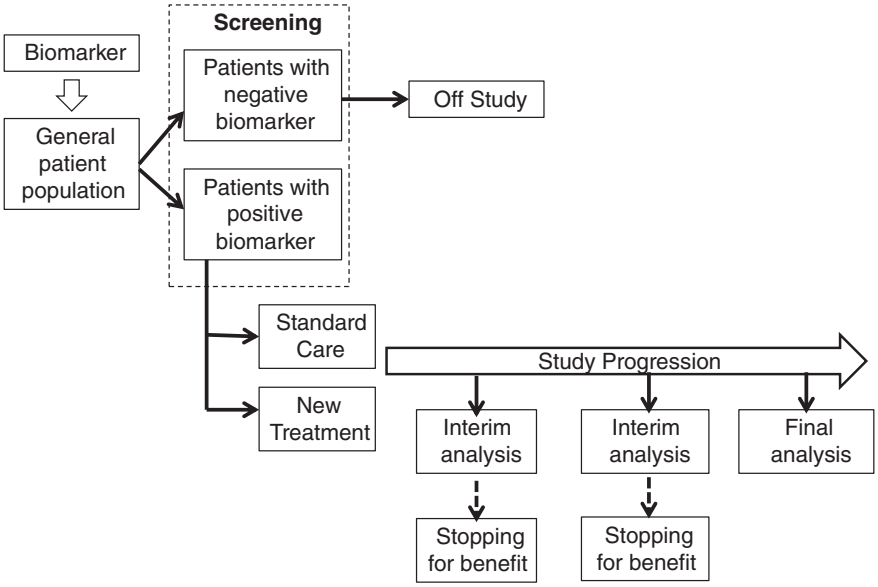

Fig. 1. Schema of multistage adaptive biomarker-directed targeted design (MAT).