

Editor's note:

The special column "Statistics in Oncology Clinical Trials" is dedicated to providing state-of-the-art review or perspectives of statistical issues in oncology clinical trials. Our Chairs for the column are Dr. Daniel Sargent and Dr. Qian Shi, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA. The column is expected to convey statistical knowledge which is essential to trial design, conduct, and monitoring for a wide range of researchers in the oncology area. Through illustrations of the basic concepts, discussions of current debates and concerns in the literature, and highlights of evolutionary new developments, we are hoping to engage and strengthen the collaboration between statisticians and oncologists for conducting innovative clinical trials. Please follow the column and enjoy.

Statistics in Oncology Clinical Trials

Overview: biostatistician's role in oncology clinical trials—strive for sound, efficient and practical studies

Qian Shi, Daniel J. Sargent

Department of Health Science Research, Mayo Clinic, Rochester, MN 55905, USA

Correspondence to: Qian Shi, PhD. Department of Health Science Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Email: shi.qian2@mayo.edu; Daniel J. Sargent, PhD. Department of Health Science Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Email: Sargent.daniel@mayo.edu.

Abstract: In this article, we highlight the role and achievement of an under-recognized group: biostatisticians who center their research and collaboration in cancer therapeutic development. By organizing a special series of invited papers from distinguished statisticians who have made significant contributions to the area of oncology clinical trials, we hope to raise the recognition of the critical roles of biostatisticians, strengthen the communication between oncologists and statisticians, stimulate more innovative research in clinical trial designs, and ultimately discover revolutionary anti-cancer treatment in the near future.

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Introduction

Although a declining mortality rate of more than 1% per year has been observed over the past ten years in western countries (1), cancers still presents great challenges to general societies and medical communities worldwide. The advances in understanding of the triangular relationship among pathway alterations at molecular level, disease prognosis at individual patient level, and treatment impact at population level bring the field into an exciting new era—target-based therapeutic development and personalized cancer medicine (2). However, in contrast to the rapid pace

of biomarker discoveries, targeted drug development is facing a frustratingly high failure rate in clinical oncology studies (3,4).

It has been a long-standing paradigm that clinical oncology studies are indeed the collaborations requiring multi-disciplinary expertise. Among these scientists, there is an under-recognized group: biostatisticians who center their research and collaboration in cancer therapeutic development. Here we provide an introduction to the topic of biostatistics in oncology research. In subsequent issues, a series of invited papers will present perspectives regarding

key aspects of clinical oncology studies from a group of biostatisticians who have made significant contributions to this area. Through this endeavor, we hope to raise the recognition of the critical roles of biostatisticians, strengthen the communication between oncologists and statisticians, stimulate more innovative research in clinical trial designs, and ultimately discover revolutionary anti-cancer treatment in the near future.

Converge of clinical and statistical reasoning

In the modern age, the word *clinical* generally refers to the care of human patients. Clinical trials are series of experimental studies aimed to search for effective treatments, compare the benefits of competing therapies, and/or establish the optimal therapeutic combinations and/or sequences of treatment. That the testing subjects are human patients is the first fact that distinguishes clinical trials from laboratory bench experiments. Genetic, behavioral and environmental heterogeneities among patients introduce great complexities in disease progresses and the impact (beneficial or harmful) of the studied treatment. While the knowledge gained by medical observation on individual patients has contributed to the advances in medicine historically, individual patient experience has proven to be not sufficient to be generalized to the population. This brings to the second distinguishable feature of clinical trials: a well-design and performed clinical trial provides generalizable inference of the tested regimen to the population level. This is mainly achieved by well-controlled and/or described person-to-person variability from known or unknown sources, and by minimizing the instrumental errors and biases through rigorous trial design and conduct.

A common view of statistics from “outsiders” is that it consists mainly of probability, or even mathematics. This is utterly not precise. As Piantadosi (5) stated “*Statistical reasoning emphasizes inference based on designed data production*”; statistics refers to the theoretical science and practical applications centered on the evidence-based inference process. The “evidence” here is not only the readouts of the data itself, but also the honest presentation of the uncertainties, and more importantly knowledge updating within the context of a scientific reasoning process. Statistical theory and methodology enables the quantifications of influence by chance, partitioning of systematic effects from random effects, controlling for bias, and generalizing the inference from selected samples to

general population, in a cost-effective manner.

Even though oncologists tackle the problems of cancer from biological point of view, whereas statisticians choose the pathway of mathematic modeling, making generalizable inferences based on observable data is indeed the essential task in both the clinical and statistical fields. The strategy of updating our knowledge of fighting cancers by combining emerging new data and existing old data, and making reliable decisions of adapting or abandoning a treatment at the population level, naturally bring oncologists and statisticians together to the same field of clinical trials. Statisticians provide the core techniques to transfer the conceptional ideas initiated by oncologists into sound and practical clinical trials throughout the entire lifetime of the study.

Clinical trial design—perspectives from a biostatistician

Since the 1940s, clinical trials have become the very center of clinical research. But not until 1970s, did the involvement of statisticians grow to be recognized in the trial methodology research due to the discussions of randomization and stratification of patients (6). Later, the increasing demands of critical and quantitative review of research design and data from regulatory, governmental funding priorities, and broader public society urged trialists to apply rigorous scientific methods to the design and conduct of clinical trials. Consequently, the scope of statistician's involvement in a particular trial reached the full spectrum, from birth to the completion of the study, and even further into subsequent cycle of hypothesis generating research. A misunderstanding regarding statistician's work in a clinical trial is to equalize it to performing data analysis. Although extensive experience in the analysis of trial data is critical, good trial design and conduct is considerably more important than final analysis. Careful attention to design is the safe guard of the final analysis and provides benefits that cannot be guaranteed or overcome by any analysis, such as simplifying and validating the analysis, controlling precision and providing sufficient statistical power upfront, permitting statistically controlled adaptations to the trial, satisfying the ethical constraints, and fulfilling the patient safety requirements (5).

Planning a clinical trial is never as simple as one task of running a sample size calculation, although this calculation does require sufficient statistical training, particularly in the area of experimental design of medical studies.

Planning a clinical trial is an interactive and iterative collaboration process between oncologists and statisticians. The conversations usually start with the dissection of the proposed hypothesis regarding a newly discovered agent or regimen. The key information a statistician will gather includes: the targeted disease population, the expected treatment effect, the most relevant endpoint, historical evidence, and allowable error rates.

For example, an oncologist may propose a hypothesis: *A newly discovered agent X will improve outcomes in advanced colorectal cancer patients with KRAS mutant tumors.* Here, the targeted population is patients with initial diagnosis of stage IV disease whose tumors present KRAS codon 12 or codon 13 mutations. The intended treatment effect may be prolonged survival time or increased disease-free rate at a given time point (e.g., three years after diagnosis). One common endpoint is progression-free survival (PFS), estimated by median time in statistical language. At this point, the statistician will rephrase the hypothesis as *agent X will increase PFS time in metastatic colorectal (mCRC) patients with KRAS mutant tumors, compared to?* The “?” here leads to the question regarding what we already know about PFS when these patients are treated with a standard of care regimen or other existing treatments. Synchronizing the information and literature data provided by the oncologist, the statistician can give a historical estimate of the median PFS time (e.g., ten months in this example from several published trials) which will serve as a benchmark for the treatment comparison. Through discussions with the oncologist, a clinical meaningful treatment effect magnitude can be solicited. For this example, extending the median PFS time from 10 to 14.3 months [corresponding to a hazard ratio (HR) of 0.75] can be considered. Hence, the statistician can further rephrase the hypothesis with statistical language: *the agent X can be considered efficacious if the HR is 0.75 or lower (lower stands for larger effect size) comparing PFS of patients with KRAS mutant mCRC tumors receiving agent X to those receiving standard care treatment.*

At this point, one might think that the statistician can wave his or her magic wand to find the sample size of the study. Unfortunately, this thought is still rather naïve. More conversations between the oncologist and the statistician regarding the study design are necessary and essential. Actually, these conversations are never just limited between two of them (statistician and oncologist). Discussions with pathologists and radiologists are valuable for rigorously outlining issues surrounding population definition and the endpoint ascertainment. Discussions with regulatory

agents and/or government funding provider strengthens the feasibility and scientific rationale of the study. Inputs from potential enrolling physicians and patient advocates bring practice and ethical considerations into the investigation. All these considerations frame the study design to be scientifically sound, yet practically feasible and efficient.

Continuing our example in mCRC patients, an underline evaluation of the study that we have not yet considered is where the development of agent X is at in the investigation process. Is it still at the very early stage, where safe doses of agent X to be administered on human subjects are unknown? Or are there sufficient safety and preliminary efficacy data, such that a confirmatory study should be carried out for final approval of usage and marketing in patient routine care? This leads to the introduction of different phases of clinical trials. Clinical trials are generally classified as phase I, II and III according to their primary aims of the drug development. Phase I studies are generally aimed to identify the optimal dose level and treatment schedules based on the assessment of toxicity of the therapeutic intervention. This kind of trial is usually small (range from 20 to 40 patients) with endpoints centered on adverse events data. In phase I trials the patient population is usually less refined than later phases of studies. The comparisons are generally self-contained within a study across different dose levels. The early efficacy signals are commonly screened for in phase II studies, with extended safety evaluation regarding the chosen dose level or treatment deliver strategy. As opposed to phase I studies, the study population is more focused (e.g., a particular tumor type with specific stage). A concrete estimate of endpoints from control population, either based on historical evidence outside of the study or including a concurrently randomized control cohort, provides the basis for treatment effect estimates (i.e., the differences in endpoint measures of the comparisons). The sample size increases to 50 to 100 patients, or more. The outcomes of phase II studies are critical to the decision of whether a large scale confirmatory study (i.e., a phase III study) is warranted or not. Phase III clinical trials are pivotal, designed to provide the definitive evidence to move a new regimen or modality into patient care, or to definitely refute the usefulness of the proposed new treatment. These studies utilize a simple and reliable tool, i.e., randomization, to prevent bias in allocating treatments in the comparison, including biases due to treatment selection based on patients' prognostic factors, and known/unknown (measured/unmeasured) confounding factors.

Within each of the phases of studies, a variety of

designs have been developed by statisticians over decades. These innovative advancements are generally motivated by a clinical need for improved methods. The continual reassessment method (CRM) (7) is an excellent illustration of moving from simple algorithm searching to sophisticated modeling in phase I dose searching studies, due to the recognition of biological dose-response effects. The urge of addressing multiple questions and efficiently incorporating internal and external pitfall data stimulated the development of adaptive designs (8). The new requirements required to investigate the treatment effects of targeted agents brought the biomarker-driven designs (9) into the field. The validation and application of surrogate endpoints enhances clinical trials in terms of the balance between reducing trial costs and maintaining valid inferences on treatment effects. These are just a few highlights in area of the clinical trial design research; each will be expanded upon in this special series of articles.

Design and conduct of clinical trials are far more complicated than experiments not involving human subjects. Ethical considerations are critical determinations of study design, monitoring and delivery of outcomes. Therefore, in addition to statistical design of clinical trials, to the series will include related topics, such as, independent data monitoring—the role of the data and safety monitoring committee (DSMC). Well-defined data collection and quality control procedures are the realizations of the trial design, and required assets for sound inferences at the completion of the study. Other topics in this special series include statistical aspects of translational and correlative studies in clinical trials, and issues in clinical trials in rare disease populations.

Conclusions

This special series will provide a state-of-the-art review/perspective of statistical issues in oncology clinical trials, and

is intended to convey statistical knowledge which is essential to trial design, conduct, and monitoring to a wide range of researchers in oncology area. Through illustrations of the basic concepts, discussions of debates and concerns, and highlights of evolutionary new developments, we are hoping to engage and strengthen the collaborations between statisticians and oncologist for conducting innovative clinical trials.

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