The Third International Workshop in Sequential Methodologies
June 14–16, 2011

Area C.9.1: Thursday, June 16, 1:30pm
Math Corner Room 380X

Speaker: Bruce W. Turnbull
School of Operations Research and Industrial Engineering, Cornell University

Title: Group sequential enrichment design incorporating subgroup selection

Abstract:
An important component of clinical trials in drug development is the analysis of treatment efficacy in patient subgroups (subpopulations). Due to concerns of multiplicity and of the small sample sizes often involved, such analyses can present substantial statistical challenges and may lead to misleading conclusions. As a confirmatory seamless Phase II/III design, we propose an adaptive enrichment group sequential procedure whereby resources can be concentrated on subgroups most likely to respond to treatment. Stopping boundaries are defined through upper and lower spending functions. The procedure is presented in terms of the efficient score, enabling the analysis of normal, binary, or time-to-event data. It addresses the dilution effect by eliminating populations at the first stage that appear likely to derive no therapeutic benefit. It subsequently proceeds with the definitive assessment of treatment efficacy among the remaining pooled populations using a group sequential design. The procedure provides strong protection of familywise Type I error rate, and we employ a bootstrap algorithm to obtain point and interval estimates that are adjusted for the selection bias. We give examples to demonstrate how the design is used. We make comparisons with adaptive two-stage combination test procedures and with a group sequential test that does not account for the presence of subgroups. Numerical results show that the procedure has high power to detect subgroup-specific effects, and the use of multiple interim analysis points can lead to substantial sample size savings.

Acknowledgement:
This is joint work with Baldur Magnusson at Cornell University.
Speaker: Sumihiro Suzuki  
*UNT Health Science Center, University of North Texas, Fort Worth*

Title: Construction of an optimal sequential plan for testing a treatment for an adverse effect

Abstract:
Sequentially planned procedures allow observations to be collected in groups of variable sizes. After every group, all the previously collected data are used to determine the next course of action. An optimal (Bayes) sequential plan minimizes the (Bayes) risk that combines the decision loss, observation cost, and group cost. In general, determining the optimal sequential plan remains an open and challenging problem mainly because it requires risk-optimization over a huge and rather unstructured set of all sequential plans. Here we demonstrate how to obtain the optimal solution for a particular class of problems that may arise in testing a treatment for a rare but severe adverse effect. This solution is obtained by studying a number of properties of the Bayes sequential plan such as transitivity and monotonicity. The proposed technique allows to reduce the search to a small manageable set of sequential plans within which the optimal plan is calculated.

Acknowledgement:
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The Third International Workshop in Sequential Methodologies  
June 14–16, 2011  
Area C.9.1: Thursday, June 16, 2:30pm  
Math Corner Room 380X

Speaker: Shyamal De  
Department of Mathematical Sciences, 
University of Texas at Dallas

Title: Sequential methods for multiple hypothesis testing with strong control of Type I and Type II familywise error rates

Abstract:  
A number of sequential statistical problems involve multiple inferences with a goal of getting a result of each individual inference instead of combining results into one procedure giving one global answer. Examples include sequential clinical trials for testing both safety and efficacy of a treatment, quality control charts monitoring a number of measures, acceptance sampling requiring several criteria, and so on. We develop sequential methods for testing multiple hypotheses, resulting in a statistical decision for each individual test and controlling the familywise error rate and the familywise power in the strong sense. Extending the classical step-up and step-down methods for multiple comparisons to sequential designs, the new techniques improve over the Bonferroni and closed testing methods proposed earlier by a substantial reduction of the expected sample size.  

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This is joint work with Michael Baron at the University of Texas at Dallas.
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Area C.9.1: Thursday, June 16, 3:00pm
Math Corner Room 380X

Speaker:  Lili Zhao  
Biostatistics Unit,  
University of Michigan Comprehensive Cancer Center

Title:  Bayesian two-stage design in Phase II clinical trials with time-to-event endpoint: A simulation-based decision-theoretic approach

Abstract:
Many statistical designs, Bayesian or frequentist, have been proposed in phase II oncology clinical trials. The majority of these are using the binary endpoint of tumor response, but failure time endpoints may not be appropriate for new cytostatic anticancer agents. These agents, in contrast to cytotoxics, are expected to delay tumor growth. Phase II evaluation of such agents may instead focus on failure time endpoints, such as time to disease progression. In this study, we propose a Bayesian two-stage design to construct stopping rules on time-to-event data in single-arm phase II trials by comparing the Bayes risk of stopping at stage one and the Bayes risk of continuing to the final stage. Simple threshold loss structures are used on time-to-event data characterized parametrically (Weibull failure time distributions are assumed) and non-parametrically. We study the properties of our designs such as power and expected run length, and compare them with the Simon two-stage designs. Costs (specifically, ratio of false rejection cost to false acceptance cost) defined in the loss function are turned to obtain desired type I and II errors and then used on a recently conducted phase II oncology trial at the University of Michigan.

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