

Tenth Annual ASA CT Chapter Mini-Conference

Emerging Statistical Issues in Clinical Trials

Conference Date: **Thursday, March 22, 2012**

Conference site: **Yale University West Campus, Orange CT**

SMART Clinical Trial Designs for Developing Dynamic Treatment Regimes

Susan Murphy, Department of Statistics, University of Michigan

The effective management of many health disorders often requires individualized, sequential decision making whereby treatment is dynamically adapted and re-adapted over time based on a patient characteristics and on response to treatment. Dynamic Treatment Regimes (DTRs) operationalize this sequential decision making via a sequence of decision rules that specify whether, how, for whom and when to alter the intensity, type, or delivery of pharmacological, behavioral and/or psychosocial treatment at critical decision points. In this talk a novel, clinical trial design (namely, sequential multiple assignment randomized trials, or SMARTs) is proposed for the purpose of developing and optimizing dynamic treatment regimes. Principles that guide the design of the SMART and potential primary analyses are discussed along with examples of SMARTs.

In this talk we discuss how a data analysis method developed for solving multi-stage decision problems in computer science, Q-learning, can be used with SMART study data to construct proposals for high quality dynamic treatment regimes. In this talk we discuss and illustrate the use of Q-Learning and provide a bootstrap based method for constructing asymptotically valid confidence sets.

Multiple Testing and Gatekeeping Procedures in Clinical Trials

Ajit C. Tamhane, Northwestern University

Multiple testing problems arise in clinical trials from many sources, e.g., multiple treatment arms or doses, multiple endpoints, interim analyses, subgroup analyses, etc. The first part of this talk will give an overview of some basic multiple testing concepts and procedures. The second part of the talk will focus on gatekeeping procedures for testing hierarchically ordered families of null hypotheses where tests on later families in the sequence are conditional on the outcomes of the tests on the earlier families in the sequence. Examples will be given from clinical trials.

An Overview of Competing Risks Data, with Applications in Clinical Trials

Jason Fine, Department of Biostatistics and Department of Statistics, University of North Carolina at Chapel Hill

This talk will survey competing risks, with an eye towards clinical trials applications. Conceptual issues related to endpoint definition will be explored, following by a discussion of standard analytic methods, including one sample estimation, two sample testing, and regression modelling. Issues related to summarizing treatment differences will be examined, including challenges in extending standard approaches for independently censored data to the competing risks setting. A primary focus will be a comparison of analyses based on the cause specific hazard and on the cumulative incidence functions. The current state of competing risks methodology in clinical trials will be reviewed, with potential areas for further development highlighted, particularly in the area of adaptive designs. Real data examples will illustrate the main points.

Multi-arm Adaptive Designs for Phase II Trials in Recurrent Glioblastoma

Lorenzo Trippa, Department of Biostatistics, Harvard University

In recent years there has been a relevant increase in the number of clinical trials and putative antiangiogenic treatments for recurrent gliomas. A substantial part of these are single arm trials. I will consider response adaptive designs comparing a control with several novel treatments. These studies are designed to progressively increase the randomization probabilities for treatments which, on the basis of the data generated in the trial, show evidence of efficacy. We compare Bayesian adaptive randomization with alternative designs including two-arm and multi-arm balanced designs. The randomization probabilities are modified adaptively by sequentially updating a Bayesian model for the outcome distributions in each arm. The probability that a patient is assigned to a specific arm depends on the updated probability (at enrollment) that the corresponding treatment is effective. Our comparison focuses on realistic scenarios defined by using historical data, including progression free survival and overall survival, from recent trials. This study quantifies advantages and disadvantages of multi-arm Bayesian adaptive trials by means of a systematic assessment of the operating characteristics and suggests conclusions that can guide design on currently planned trials in glioma.

Regression modelling of the cumulative incidence function with missing causes of failure using pseudo-observations

Aurelien Latouche, Conservatoire national des arts et metiers, Paris, France

Methods for estimating the effects of prognostic factors on the risk of death from a given cause often assume that the cause of death is known for all patients. Exclusion of individuals with missing cause of death information might lead to biased estimates. Some authors have proposed methods taking into account the missing cause of death mechanism, particularly for modelling the cause-specific hazards. However, little attention has been given to direct modelling of the cumulative incidence function which is of prime interest with competing risks. The rationale for the present work is to derive a flexible class of regression models for the cumulative incidence function when there are missing causes of failure, encompassing key models such as the Fine and Gray and additive models. More precisely, we propose two approaches that extend the Andersen-Klein framework to the missing cause setting. The first approach is grounded on the inverse probability weighting paradigm for dealing with missing data and the second is a multiple imputation method tailored for the Andersen-Klein model. We illustrate both approaches by analyzing the data from the ECOG 1178 breast cancer treatment clinical trial.