**Workshop in Phase I Designs with a Focus in the Continual Reassessment Method**

**October 2nd, 2009**

**Memorial Sloan Kettering Cancer Center, New York, NY**

**Location: 307 E. 63rd Street, 3rd floor conference room**

**New York, NY 10065 (Tel. 646 735 8100)**

**Program:**

8:30am: Breakfast

8:50am: Opening Remarks by Alexia Iasonos

1. 9:00am. John O’ Quigley, University of Virginia

Title: Bayesian model selection for generalized CRM models

The techniques outlined by Gelfand and Dey (JRSSB 1994) for choosing over a small discrete set of models can be applied to generalized CRM models. Note that, typically, the CRM models themselves are underparametrized. Specifically, we can expand the CRM set of models to consider more general situations. We look at two particular problems; (1) the problem of subject heterogeneity and (2) the multidrug problem in which we only have partial orderings.

1. 9:40am. Peter F. Thall, Department of Biostatistics University if Texas, M.D. Anderson Cancer Center

Title: Utility-Based Optimization of Combination Therapy Using Ordinal Toxicity and Efficacy in Phase I/II Clinical Trials

A Bayesian outcome-adaptive design is proposed for choosing the optimal dose pair of two agents used in combination in a phase I/II clinical trial. Patient outcome is characterized as two ordinal variables accounting for toxicity and treatment efficacy. A generalization of the Aranda-Ordaz model (1983) is used to express each marginal outcome probability as a function of dose pair, and a Gaussian copula is assumed to obtain a joint distribution. Numerical utilities of patient outcomes were obtained from a group of medical oncologists using an iterative elicitation method designed to establish consensus. During trial conduct, a dose pair is chosen for each successive patient cohort to maximize the current posterior mean utility, subject to safety constraints. The method is illustrated by a trial of a chemotherapeutic agent and a biologic agent for treatment of bladder cancer, including a computer simulation study.

1. 10:20am. Ken Cheung, Columbia University

Title: Model Calibration in the CRM

The continual reassessment method (CRM) is a model-based dose-finding design. Briefly, a CRM model has of three components: the functional form of the dose-toxicity curve, the prior distribution of the model parameter, and the initial guesses of the toxicity probability associated with the test doses. While the method has been shown to be consistent under model misspecification, some models are better than the others. However, since there are infinitely many possible ways to specify each of the three components of a CRM model, the calibration process, typically done by trial-and-error in practice, can be complicated and time-consuming. In this talk, we present various model calibration perspectives and take a pragmatic approach to obtain a CRM model that will yield competitive operating characteristics over a wide range of scenarios.

1. 11:00am. Ying Yuan, M.D. Anderson Cancer Center

Title: Bayesian Model Averaging Continual Reassessment Method in Phase I Clinical Trials  
                                     
The continual reassessment method (CRM) is a popular dose-finding design for phase I clinical trials. This method requires practitioners to  prespecify the toxicity probability at each dose. Such prespecification can be arbitrary, and different specifications of toxicity probabilities may lead to very different design properties. To overcome the arbitrariness and further enhance the robustness of the design, we propose using multiple parallel CRM models, each with a different set of prespecified toxicity probabilities. In the Bayesian paradigm, we assign a discrete probability mass to each CRM model as the prior model probability. The posterior probabilities of toxicity can be estimated by the Bayesian model averaging (BMA) approach.  
Dose escalation or de-escalation is determined by comparing the target toxicity rate and the BMA estimates of the dose toxicity probabilities. We examine the properties of the BMA-CRM through extensive simulation studies, and also compare the new method and its variants with the original CRM. The results show that our BMA-CRM is competitive, robust, and eliminates the arbitrariness of the prespecification of toxicity probabilities.

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11:40 - 12:30 Lunch Break

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1. 12:30pm. Tom Braun, University of Michigan

Title: Incorporating Patient Heterogeneity in Adaptive Phase I Trial Designs.

Existing models for adaptive Phase I designs assume that the probability of DLT by the end of follow-up is the same for every subject receiving the same dose.  However, patients enrolled in Phase I trials vary greatly in their current disease status, numbers and types of previous chemotherapy/radiation treatment, and many other factors that would impact their likelihood of DLT beyond that explained by dose.

We examine two extensions to the CRM, a frailty regression model and a hierarchical Bayesian model, for incorporating patient heterogeneity into the dose assignment algorithm. We give theoretic and simulation-based results describing the operating characteristics of both models in terms of identifying the correct maximum-tolerated dose and the probability of overdosing patients.  One important aspect for these models is correctly modeling the extent of heterogeneity and we examine how an incorrect heterogeneity model can impact the operating characteristics of both models.

1. 1:10pm. Sarah Zohar, Hopital Saint-Louis, France

Title: Sensitivity Study of Dose Finding Methods

We investigate the reliability of conclusions from dose finding designs such as the continual reassessment method (CRM, O’Quigley et al. 1990) when certain arbitrary model parameters are modified. The purpose of these designs is to locate the MTD (maximum tolerated dose, in practice a dose with some give acceptable rate of toxicity). The model based designs aim to carry out this prescription in an efficient way. However we need bear in mind that there are a number of arbitrary features in the choice of any particular model. Here we investigate what happens for small samples since, in practice, these designs will often include no more than 16 to 20 patients. A key question is the following. Would we have made the same recommendation concerning the MTD had we worked with a design specified differently? If we are to consider a broad class of designs, then how does the choice of a member from this class impact the final result? A design is considered to be robust for small samples if the choice of arbitrary parameters has a negligible impact on the final recommendation. A second component of this study is to investigate how sensitive is in trial allocation and final recommendation to errors in the responses. Certain toxicities may go undetected and, conversely, certain non-toxicities may be incorrectly recorded as dose limiting toxicities. Intuitively we anticipate any such errors to impact the results since these only depend on the accumulated observations. The question is how large can these errors be before the final results must be deemed quite unreliable.

7. 1:50pm. Liz Garrett-Mayer, Medical University of South Carolina

Title: Continual Reassessment Models for Ordinal and Multivariate Outcomes

The original CRM was designed with a binary measure of toxicity in mind. In recent years, Phase I dose-finding trials have expanded where optimal dose is not chosen based simply on dose-limiting toxicities. Targeted agents in cancer research frequently have very low toxicity rates (even at high doses) and dose finding needs to guided by measures of immunologic response or pharmacodynamic outcomes. In these cases, ordinal or categorical classes of response are of interest and CRM designs for these scenarios should be implemented. Even in cases where toxicity is not anticipated to be a concern, designs still need to accommodate the possibility of adverse events and dose-limiting toxicities in their escalation approaches. A number of designs that may apply in a variety of these settings have been developed and we will discuss, compare and contrast them. Included will be the continuation ratio CRM model (Mandrekar et al., 2006) and a proportional odds CRM model (Van Meter, 2009).

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2:30- 2:40 Break

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8. 2:40pm. Glen Laird, Novartis

Title: Estimation with Overdose Control Implementation at Novartis Oncology   
  
Various implementations at Novartis of Bayesian logistic regression (BLR) guided by the Escalation with Overdose Control (EWOC) criteria for dose escalation studies will be discussed. These models explicitly control the probability of overdosing throughout dose escalation (in the interest of patient safety) while maintaining reasonably good performance in the targeting of the maximum tolerated dose (MTD) . Comparisons via simulation with the 3+3 and CRM/MCRM methods are reviewed. Pragmatic aspects of the BLR-EWOC including evaluation of new therapies as single-agent and/or in combination, multiple dosing schedules, flexible cohort sizes and incorporation of relevant covariates are presented. Some practical experiences with the model in clinical trials are discussed along with model extensions for potential use in future trials.

9. 3:20pm. Xiaobu Ye, Sidney Kimmel Cancer Center, Johns Hopkins University School of Medicine

Title: Practical implementation of CRM in real clinical settings for oncology dose-finding trials

It has been two decades since the CRM method was first introduced to the public by O’Quigley et al. The adaptation of CRM method in current oncology dose-finding trials, however, is still uncommon, at only about 4%. One of the challenges in applying the method is how to practically implement it, to make it easily conducted by statisticians, and to be accepted by physicians who are running the trials. Based on our experience of using modified CRM method in dose-finding trials conducted through the New Approaches to Brian Tumor Therapy (NABTT) consortium, the talk will demonstrate how to implement the modified CRM method using appropriate practical procedures and the free CRM software developed and provide by Dr. Steven Piantadosi. Certain challenges will be discussed with regard to the new anticancer drug paradigm of molecularly targeted agents.

10. 4:00 Satoshi Morita, Yokohama City University, Japan

Title: Practical application of the continual reassessment method to a phase I dose-finding trial in Japan: East meets west.

We present a practical application of a continual reassessment method (CRM) to a phase I study identifying the recommended dose level of chemotherapy in patients with advanced breast cancer. First, we conducted a preliminary study to determine a prior distribution for a model parameter to be used in the CRM, based on pre-study perceptions of a panel of oncologists. We analyzed sixteen patients three of whom experienced a dose limiting toxicity. The dose-toxicity curve was updated based on observed toxicity data. The recommended doses were very similar to those identified in a previous dose-escalation study conducted in Europe using a conventional ‘3+3’ cohort design.

11. 4:40pm. Alexia Iasonos, Memorial Sloan Kettering Cancer Center

Title: Estimating the dose-toxicity curve in completed phase I studies

It has been shown previously that the MTD chosen by the standard method (SM) may be low, possibly leading to a non-efficacious dose. Additionally, when deviation from the original trial design occurs, the rules for determining MTD might not be applicable. We hypothesize that a retrospective analysis would suggest a MTD that is more accurate than the one obtained by the SM. In this study, we propose a method to analyze completed phase I trials and possibly amend the recommended Phase II dose, based on constrained maximum likelihood estimation (CMLE). I will present a comparison of CMLE with the retrospective Continual Reassessment Method (O’Quigley 2005) in analyzing simulated SM trials as well as existing trials from Memorial Sloan Kettering Cancer Center. A framework for estimating confidence intervals around the toxicity probabilities at each dose level will also be presented. This is joint work with Irina Ostrovnaya.