

ADAPTIVE DESIGNS FOR DOSE FINDING

a 1-day course by

Inna Perevozskaya, Yevgen Tymofyeyev, and Jim Bolognese
from Merck Research Labs

Friday September 12, 2008

9:00 – 5:00

Holiday Inn, Fort Washington

432 Pennsylvania Ave., Ft. Washington, Pa. 19034

Phone 215-643-3000

REGISTRATION INFORMATION

Cost: \$65 (\$25 full-time students)

Registration: Please [go here](#) to register and pay in advance by Friday, September 5 to assist with the head-count.

Registration 8:30 - 9:00. Class begins at 9:00. Coffee and danish, buffet lunch, and afternoon beverages will be provided.

Directions: From the PA Turnpike, take Exit 339 – Fort Washington. After the tollbooth, follow the left-hand lane under the overpass. (DO NOT TAKE THE ROUTE 309 RAMP.) The hotel is 1/8 mile on the left. From Route 309, take the Fort Washington exit. (DO NOT TAKE THE EXIT FOR THE PA TURNPIKE.) Exiting will put you onto Pennsylvania Avenue. Stay in the left-hand lane. The hotel is 1/8 mile on the left.

COURSE ABSTRACT

There is increasing interest in applying adaptive designs (AD) to increase efficiency of clinical trials. AD are trials which use accumulating information during the trial to alter study design features in pre-planned algorithms to improve performance characteristics. AD can yield similar or better information than traditional fixed design trials while using fewer patients and/or shorter study conduct time. One cost for these trials is more complexity in design, conduct, and/or analysis. This course covers AD for dose-finding in the early development Phase I/II space. The introduction includes definitions and classification of adaptive designs. This is followed by 4 Sections on AD for oncology, dose-finding for true underlying monotonic dose-response relationships, dose-finding for U-shaped ("umbrella") dose-response relationships, and demonstration of software for

design of these trials. Dose-finding designs covered include both frequentist and Bayesian types. Participants will receive a broad overview of AD and examples as well as references for additional technical details. This will provide an in-depth orientation to AD for dose-finding so participants can begin to explore them on their own.

COURSE OUTLINE

1. Introduction (1hr, Inna)
 - 1.1. Definition
 - 1.2. Classification (includes G-S; very abbreviated version of Vlad's paper)
2. Oncology (1½hr; Yevgen)
 - 2.1. Objectives and goals (early toxicity, MTD)
 - 2.2. 3+3
 - 2.3. CRM
 - 2.4. Modified Ji's design
 - 2.5. Examples and simulations
3. Dose-ranging for general monotonic response (2hrs; Jim&Inna)
 - 3.1. Objectives & goals: combined POC and D-R for efficacy
 - 3.2. up-and-down
 - 3.3. t-statistic
 - 3.4. D-optimal (Inna)
 - 3.5. Berry-type 4-param logistic
 - 3.6. dose-adaptive X-over (Kristels+Inna's slides merged)
 - 3.7. Examples and comparison
4. Dose-ranging for U-shaped (umbrella) dose-response (1½ hr; Yevgen)
 - 4.1. Objectives & goals: combined POC and D-R for efficacy& safety combined (utility function reflects both)
 - 4.2. slope method
 - 4.3. NDLM
 - 4.4. 2-stage
 - 4.5. Examples and comparisons
5. Software Demo (2-nd priority, if time permits)
 - 5.1. link to D-opt
 - 5.2. MD-Anderson
 - 5.3. Cytel
 - 5.4. Decimaker

BIOSKETCHES

James A. Bolognese, MStat
Senior Director, Scientific Staff
Experimental Medicine Statistics
Merck Research Labs
Rahway, NJ 07065

Jim joined Merck in 1976 after his BS in math from Bucknell University and MStatistics from University of Florida. He worked 4 years on late phase clinical research projects across several therapeutic areas, followed by 10 years on clinical pharmacology projects, 4 in pre-clinical statistics, and then 10 on late phase coxib projects. In early 2005, he was appointed head of Merck's experimental medicine statistics group which now includes 7 statisticians.

Jim has worked and published on dose-adaptive designs in clinical pharmacology in the 1980's, and now as part of his experimental medicine statistics role is studying and assisting in implementation of dose-adaptive designs to accomplish proof-of-concept and dose-ranging objectives in a single study. Additionally Jim has designed and served as blinded statistician on the steering committees of two large outcomes trials.

Inna Perevozskaya, Ph.D.
Associate Director, Scientific Staff
Late Development Statistics
Merck Research Laboratories, Rahway, NJ

Inna Perevozskaya has been with Merck since 2001 supporting late stage development clinical trials in atherosclerosis and cardiovascular therapeutic areas. Since November 2007, she became a core member of Adaptive Design Support group within Merck. Her research interests are focused on novel designs for clinical trials in the early development stages, specifically adaptive dose-finding trials. Inna is a member of the American Statistical Association and Drug Information Association; she is also actively involved in PhRMA Working Group on Adaptive Designs. Her research works received Thomas Teal Award for best statistical paper published in DIJ in 2005. She holds a PhD degree in Statistics from University of Maryland Baltimore County (2001) and a MS degree in Applied Mathematics from Moscow State University, Moscow, Russia (1995).

Yevgen Tymofyeyev, Ph.D
Senior Biometrician, Scientific Staff
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Yevgen Tymofyeyev earned his Ph.D in Statistics and received an M.S. in Applied Mathematics from the University of Maryland Baltimore

County. He joined the Biometrics Research Department at Merck in 2005 and has worked on image analysis, biomarkers validation, and statistical analysis of EEG data. Starting from July 2007, Yevgen has been responsible for support of adaptive design studies at Merck, working on several trials and developing methodology and software for dose-ranging, two stage, dose finding in oncology and group sequential designs both frequentist and Bayesian type. Yevgen's research interests include statistical computation, novel designs for clinical trials, response-adaptive randomization and optimization.