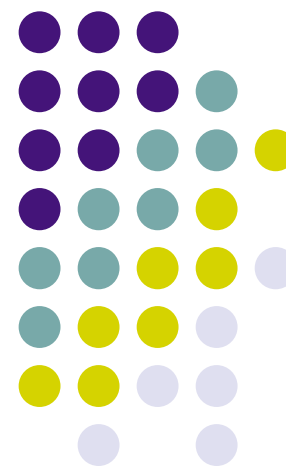


Adaptive Design: Where Are We Now?

Panel Discussion, JSM 2009

Cyrus R Mehta, Ph.D.
President, Cytel Inc.

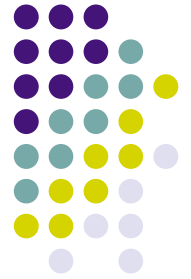


Importance of Seamless Phase 2/3 for Population Enrichment Designs



- 45% of all compounds and 60% of all oncology compounds fail at phase 3 (Kola & Landis, *Nature Reviews*, 2004)
- New scientific advances to reduce attrition
 - Advances in human genomic studies
 - Molecularly targeted therapies
 - Methodology of phase 2/3 design

Proliferation of Predictive Biomarkers for Monoclonal Antibodies



1. **Non-Small Cell Lung Cancer:** 65% response rate with EGFR mutations vs 5% without, if treated with erlotinib (Jackman, ASCO, 2009)
2. **Colorectal Cancer:** 23% response rate with KRAS wild-type vs 0% with KRAS mutations, if treated with cetuximab (Souglakos, *Br. J. Cancer*, 2009)
3. **Breast Cancer:** 0.53 HR with high Ki-67 labelling index, versus 0.81 HR with low Ki-67, if treated with letrozole (Viale, JCO, 2009)

Golden Opportunity for Statisticians to Design more Innovative Trials



- Current biomarker data was all obtained in retrospective analyses
- Useful only for formulating hypotheses
- Adaptive phase 2/3 methodology:
 - directly applicable to population enrichment
 - could confirm predictive hypotheses
 - could increase statistical power
 - targeted therapies directed at right population

Prospective Population Enrichment in II/III Design



- Start out by opening enrollment to the broader population with and without the biomarker
- At interim look, restrict enrollment to the subgroup that appears to benefit
- Methodology Papers:
 - Wang, O'Neill, Hung (*Pharm. Stat.*, 2007)
 - Friedlin & Simon (*Clin. Cancer Res.*, 2005)
 - Brannath et. al. (*Statist. Med.*, 2009)
 - Mehta et. al. (*Circulation*, 2009)

Two Examples of Recent Population Enrichment Trials



- **Cancer Trial by Novartis.** Time to event end-point. Start out with full population, use Bayesian decision rules to drop non-responsive subgroup.
 - Brannath et. al. *Statist. Medicine*, 2009
- **Cardiology Trial by The Medicines Co.** Binomial endpoint. Start out with full population, drop non-responsive subgroup based on low conditional power.
 - Mehta et. al. *Circulation*, 2009

Parameter Estimation in Adaptive Trials



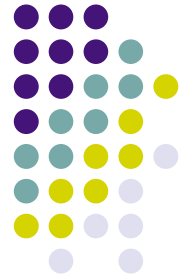
- Minimum Requirements
 - Confidence interval should provide the desired coverage -- if not **exactly** than **conservatively**
 - Point estimate should avoid bias if possible. If not possible, then bias should be **negative** when estimating treatment benefit and **positive** when estimating treatment harm

Two Methods for Adaptive Group Sequential Trials



- RCI Method: Generalize the Repeated Confidence Intervals approach of Jennison and Turnbull (*JRSS B*, 1989).
 - Mehta, Bauer, Posch, Brannath (*Stat. Med.* 2007)
- SWACI Method: Generalize the Stagewise Adjusted Confidence Intervals approach of Tsiatis, Rosner and Mehta (*Biometrics*, 1984)
 - Brannath, Mehta, Posch (*Biometrics*, 2009)

Comparison of the Two Methods



- Both meet the minimum requirements. But RCI method is conservative and SWACI method is exact

Spending Function	True δ	Actual Coverage of 95% CI		50th Percentile of $\delta_{0.5}$	
		SWACI	RCI	SWACI	RCI
$\gamma(-4)$	0.0	0.95116	0.94974	-0.000110	-0.000403
$\gamma(-4)$	0.1	0.94937	0.96120	0.099888	0.099939
$\gamma(-4)$	0.2	0.94995	0.97827	0.199991	0.188232
$\gamma(-4)$	0.3	0.9502	0.98984	0.299609	0.252511

- Based on 100,000 simulation o a two-stage design. (Brannath, Mehta, Posch, *Biometrics*, 2009)