
Case Study of a Flexible Adaptive Design

PhRMA Adaptive Design Workshop
Bethesda, MD

November 13, 2006

Cyrus R. Mehta

President, Cytel Inc.

email: mehta@cytel.com – web: www.cytel.com – tel: 617-661-2011

Background on the Integrated Phase II/III Trial

The standard practice is to run two separate trials

- Run a Phase II multi-arm trial comparing several doses and a placebo
- Review results upon completion of Phase II
- Run a Phase III trial with one or two Phase II doses plus placebo

The Problem with Running Two Separate Trials

- The data from Phase II cannot be combined with the data from Phase III
- Excessive administrative time delay between terminating Phase II and activating Phase III

In some situations it might be more efficient to run one integrated Phase II/III trial

Case Study: a CNS Trial

- Continuous outcome; observed after four weeks therapy
- Randomized to five regimens of daily dose (10mg, 50mg, 150mg, 300mg, 450mg) or placebo
- Designed for five pairwise comparisons against placebo
- Require 90% power on a two-sided level-0.05 test to detect a difference of $\delta = 1.7$
- Estimated standard deviation is $\sigma = 4$

Factors Favoring an Adaptive Design

- Relatively quick endpoint; at the end of four weeks
- Relatively slow enrollment; 10 subjects/week

Thus it is feasible to make an adaptive change before the enrollment phase is completed

Two-Stage Adaptive Design

- Enroll 50/arm at Stage 1. Then, based on **pre-specified decision rules**:
 - Drop up to three doses for futility
 - Re-estimate sample size for doses continuing to Stage 2
- Enroll the required number of patients for Stage 2
- At end of Stage 2 identify the statistically significant doses using appropriate adjustments for **adaptive changes in sample size** and **multiple comparisons**

Decision Rules for Increasing Sample Size

- Do not increase sample size above 250/arm
- Do not reduce the sample size
- Base the sample size increase on **conditional power** of the arm that is performing the best at the interim analysis

Conditional Power Criteria

Conditional power (CP) is the probability, **given the interim results**, that statistical significance will be achieved at the end of the trial.

Rules for Sample Size Change

For the treatment arm that is doing the best:

Very Promising: If $CP(170) \geq 90\%$, then set $N = 170$ per dose group

Promising: If $CP(170) < 90\%$ and $CP(250) > 90\%$, set N so that $CP(N) = 90\%$

Hopeful: If $50\% \leq CP(250) \leq 90\%$ set $N = 250$ per dose group

Hopeless: If $CP(250) < 50\%$, consider terminating trial for futility

Decision Rules for Dropping Arms

- Once N has been determined, drop any arm if $CP(N)$ is less than 50%
- No more than three arms should be dropped
- Do not drop a higher dose if a lower dose is continuing

These rules can be overruled if safety considerations arise

Statistical and Operational Problems

- **Special statistical methods are needed:**
Otherwise the type-1 error might be inflated by the adaptive changes
- **Special operational procedures are needed:**
Otherwise the clinical investigators might gain access to the unblinded interim results

Protection Against Inflation of Type-1 Error

- Combine the p-values from Stage 1 and Stage 2 by **inverse normal weighting** to accommodate the data dependent sample size change
- Use a **closed testing procedure** to accommodate the multiple comparisons of treatment versus placebo

Combining the P-Values

For testing hypothesis H_j : dose- j is no better than placebo:

$(p_j^{(1)}, p_j^{(2)})$ = the p-value based on (Stage-1, Stage-2) data

$(n_j^{(1)}, n_j^{(2)})$ = **pre-specified** sample size for (Stage-1, Stage-2)

The **combined p-value** from both stages is:

$$p_j = 1 - \Phi \left\{ \sqrt{\frac{n_j^{(1)}}{n_j^{(1)} + n_j^{(2)}}} \Phi^{-1}(1 - p_j^{(1)}) + \sqrt{\frac{n_j^{(2)}}{n_j^{(1)} + n_j^{(2)}}} \Phi^{-1}(1 - p_j^{(2)}) \right\}$$

Handling Dropped Doses and Multiple Comparisons

For doses that are dropped at Stage-1, assign a combined p-value of 1. Then:

1. Order the five p-values in descending order, and denote them by $p_{[1]} \geq p_{[2]} \geq \dots p_{[5]}$
2. If $p_{[1]} \geq \alpha/1$, accept $H_{[1]}$ and proceed to test $H_{[2]}$
3. If $p_{[2]} \geq \alpha/2$, accept $H_{[2]}$ and proceed to test $H_{[3]}$
4. In general accept $H_{[j]}$ if $p_{[i]} \geq \alpha/i$, $i = 1, 2, \dots, j$

This is the Hochberg closed testing procedure for preserving the overall α

Importance of Simulation

Often the simulation software must be submitted along with the protocol design for regulatory review. They are needed:

- To verify that the type-1 error is preserved
- To evaluate operating characteristics:
 - power
 - probability of dropping each dose
 - average sample size
- To fine-tune the decision rules if they are unsatisfactory

Simulate the Adaptive Design

Simulation of Seamless Phase II/III Design

# of Arms (Excluding Placebo)	5
2 * 1-sided Overall Alpha	0.05

Simulation Parameters						
	Placebo	Trtm1	Trtm2	Trtm3	Trtm4	Trtm5
Mean	0	0	0	0	0	0
Std. Dev.	4	4	4	4	4	4

	Hypothesis Rejected						All Accepted
	H1	H2	H3	H4	H5	At Least One	
Count							
%							

	Treatments Dropped						
	Trtm1	Trtm2	Trtm3	Trtm4	Trtm5	None	All
Count							
%							

Average Sample Size Per Arm						Overall Average
Placebo	Trtm1	Trtm2	Trtm3	Trtm4	Trtm5	

Total Simulations	10000
Current Simulations	

Difficulties with Pre-Specification of the Adaptive Rules

- Factoring-in safety?
- Combining interim results with external data?
- Anticipating all possible contingencies (clinical, as well as business related) that might justify an adaptive change; conditions might be different at the time of the interim analysis

Regulatory Practice

- It seems reasonable to examine all aspects of the interim data concerning efficacy and safety before deciding which doses to drop or how much to increase the sample size
- The statistical methodology supports making such adaptations **without** pre-specification of the adaptive rules
- However, regulatory restrictions preclude this level of flexibility. The entire adaptive strategy must be pre-specified and written into the Interim Analysis Charter

Emerging Operational Procedures

- **An Independent Statistical Center performs the interim analysis and functions in accordance with an Interim Analysis Charter**
- **Recommended adaptative changes are communicated to sponsor and DMC**
- **Efficacy and safety results are are communicated to DMC as usual**

Interactions with the FDA

- **A special protocol assessment (SPA) to review the adaptive design is highly recommended. The FDA is required to respond within 45 days**
- **In addition to theoretical arguments, adaptive simulations that demonstrate that the overall type-1 error is preserved despite the data dependent sample size change should be made available to the FDA**

A Final Take-Away Message

Adaptive trials require a considerable amount of planning up-front. **One of the most versatile tools for the planning phase is simulation**

- The simulations clarify the risks and benefits of the proposed approach by putting probabilities on each possible outcome
- The simulations facilitate better communication with the FDA
- The simulations facilitate greater communication between the various members of the study team by showing how different design options and trial outcomes will have different implications for:
 - patient recruitment
 - drug supply
 - economic analyses
 - clinical outcomes
 - statistical power
 - regulatory concerns