

Data Monitoring Committees and
Adaptive Clinical Trial Design
Medical Device Considerations

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Problems With Medical Devices and Clinical Trials

- Cultural
 - Devices have evolved from simple tools to complex implants
 - Evaluation has also evolved with complexity of devices, but there is no uniformity of consensus across the device arena
 - Cardiovascular devices lead the way with RCTs, ortho/spine and neurological devices are further behind.
- Devices are operator dependent
- Devices are often evaluated without masking
- Device implants may have an initial “trial” testing period
 - Where does one randomize?

Problems With Medical Devices and Clinical Trials

- Device development moves from pilot to pivotal, without a classical “Phase II” trial
 - Small “start-ups” over-estimate treatment effects
- Rapid iterations and shortened total product lifecycle
 - Frequent minor improvements that are perceived to have clinical relevance (ease of use, smaller, cheaper) but arguably do not substantially alter the basic safety and efficacy characteristics.
- A legitimate new (third) arm may be available for study after randomization begins

Motivation for Adaptive Methods

- Evaluation of frequent new device iterations
- Many, if not most, trials suffer from unrealized pre-specified conditions that will affect proper execution, validity and new treatment success in clinical trials
- Device trials are especially vulnerable to unpredictability
 - Investigator and commercialization pathways often involves small groups/companies with limited resources and suboptimal methods for estimating superior critical trial parameters
 - Rapid technology turnover and shortened total product lifecycles may over-accelerate clinical trial evaluations for larger sponsors

Motivation for Adaptive Methods

- Ethical and efficiency considerations
 - “The optimum sample size is defined as the minimum number of subjects required to confidently determine the actual effect size of the primary endpoint, while ensuring that there is enough data to also determine the relative safety of the test treatment...” (Golub, HL Stat Med 2006;25:3231).
 - Scarce resources employed in expensive clinical trials should be utilized to reduce aborting of ongoing clinical trials
- Avoidance of non-pre-specified “salvage” fixes
 - Type I error control is difficult to estimate, interpretation of results are not clear

The Predicament of Randomized Clinical Trials

Pre-specifications are not always correct

- Pre-specified requisite conditions for successful execution of a valid clinical trial
 - Predictable Reference population characteristics
 - Target population must be well-defined under the impact of the trial
 - Sample group should have predictable variances and rates in terms of principal endpoints under the null hypothesis (Standard of Care)
 - Predictable new treatment characteristics
 - Unknown existence of low rate major adverse events
 - Unknown magnitude of placebo effect from prior studies
 - Predictable enrollment rate
 - Maximizes the use of resources to achieve optimum enrollment density

The Predicament of Randomized Clinical Trials

Pre-specifications are not always correct

- Pre-specified requisite conditions for successful execution of *winning new treatment trial*
 - Predictable Reference population characteristics
 - Target population must be well-defined under the impact of the trial
 - Predictable treatment effect and safety performance of the candidate therapy (device) under the alternative hypothesis (new therapy works)
 - Predictable new treatment characteristics
 - Unexpected adverse events must be measurable and controlled
 - Prior observed treatment effect must exceed true treatment effect *plus* any discounted treatment effect expected from masking methods
 - Predictable enrollment rate
 - Enrollment must be brisk to support consensus of equipoise

Prophylaxis and Remedies for Unpredictable Clinical Trial Conditions

Which should be addressed by adaptive methods?

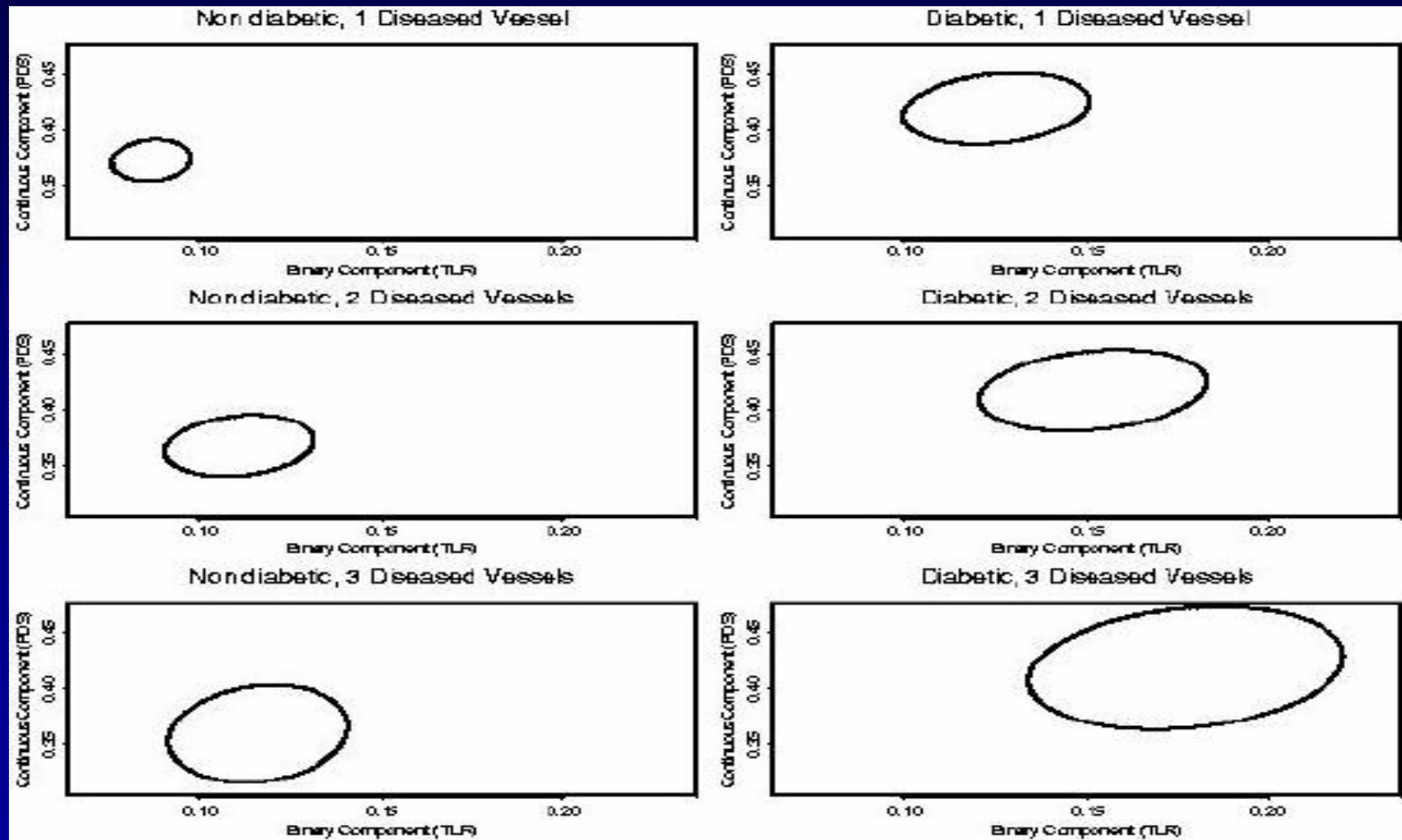
- **Unstable requisite conditions for successful execution of a *valid clinical trial***
 - Seeks to stabilize critical “null” conditions: Control rates and variances
 - Least likely to introduce bias and inflated type I error of estimating treatment effect
- **Unstable requisite conditions for successful execution of *winning new treatment trial***
 - Likely not as important as control of primary validity conditions
 - Addressed well by conventional group sequential analyses
 - Often requires pre-specifying the lowest acceptable rate of success that has “clinical” significance.
 - **Curiously, many “adaptive” designs focus on this component**

Remedies for Frequent Iterative Device Changes

- Establish major and minor change thresholds for device iterations
 - Large changes: RCTs
 - Small changes: Single arm studies
- Single arms studies for small device changes
 - Use advanced statistical approaches to estimate the historical control performance criteria
 - Test the prospective data against these performance criteria
 - (Grunkemeier GL, Johnson DM, Naftel DC. Sample size requirements for evaluating heart valves with constant risk events. J Heart Valve Dis. 1994;3:53-8)
 - Bayesian Models

Figure: Bivariate OPC for six types of patients.

This is constructed using a Binary outcome TLR and a continuous measures of restenosis (Fusten270). A multivariate statistical model must be fit to the data to establish **OPC** involving two or more endpoints.



O'Malley AJ, Normand SL, Kuntz RE. Application of models for multivariate mixed outcomes to medical device trials: coronary artery stenting. *Stat Med* 2003;22:313-36

Potential Remedial Agents

Sponsor

Investigators

✓ *Data and Safety Monitoring Committee*

- Major mandates: Subject safety and trial validity
- Minor mandates: Resource economy, trial efficiency, variable sponsor sensitivity
- Governance: Formal and informal rules and oversight
- Authority: Variable

Potential Remedial Tools

- Clinical Trial Design Engineering
 - Classical Group sequential analysis
 - Underutilized?
 - Early estimates of the endpoints are viewed with high degrees of uncertainty, and the initial trial design is largely protected
 - Requires large investment lay-out that may be trimmed back
 - Newer “Adaptive” clinical trial designs
 - Too flexible?
 - Early estimates of the endpoints are viewed with high degrees of certainty which lead to changes in trial parameters (sample size, etc.)
 - Allows for smaller initial investment, but may send a message with trial expansion

Questions for the Panelists

- 1) Should there be more effort in developing consensus regarding levels of iteration of new devices so that more simple single arm trials may be used that employ advanced observational statistical techniques to estimate historical performance?
- 2) Are early endpoint estimates in randomized clinical trials viewed differently, with respect to certainty, under classical group sequential methodology versus newer adaptive designs?

Questions for the Panelists

- 3) Can the perceived need for using more adaptive clinical designs be met largely by using more traditional group sequential methods?

- 4) Is adaptation for wrong assumptions of control arm performance (under the null hypothesis) a more worthy goal than adaptation for wrong assumptions of device performance?
 - Wouldn't adaptive designs to avoid wrong control group assumptions force sponsors to design a trial size for the smallest clinically important effect (SCIE)?