Adaptive Sample Size Re-estimation: Design and Inference

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Disclaimer

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Outline

1. Statistical Efficiency of Adaptation
2. Complete Inference after Adaptation
   - Inference for Pre-specified Design
   - Inference after Unplanned Adaptation
3. Evaluating Inferential Methods
4. Additional Issues

1. Statistical Efficiency of Adaptation

2. Complete Inference after Adaptation
   - Inference for Pre-specified Design
   - Inference after Unplanned Adaptation

3. Evaluating Inferential Methods

4. Additional Issues

Competing Issues in Clinical Trials

- Ethics: individual and collective
- Clinical science: overall patient health
- Basic Science: mechanisms
- Statistical: reliable and precise answers
- Economic/Operational: feasibility, profits and/or costs

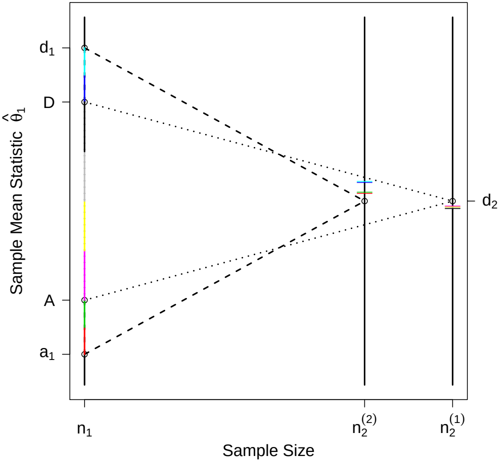
Considering Adaptation

- What do we gain?
  - Efficiency?
  - Flexibility?
- What do we lose?
  - Efficiency?
  - Interpretability?
  - Ease of implementation?
- How do we make fair comparisons?
  - Same number or schedule of analyses, or trial duration?
  - Same power at the alternative? Same power curve?
  - How to measure efficiency?

Efficiency of Adaptive Testing

- Methods of adaptive hypothesis testing based on combination or conditional error functions violate sufficiency principle
    - Same sample mean and N at stopping could lead to opposite decisions (see next slide)
- Suffer efficiency losses compared to GSDs
    - Losses of $\sim$ 40% in certain cases (Jennison and Turnbull 2006)
- Efficiency loss due to testing method or poor sample size modification rules?

Violation of Sufficiency Principle



Our Research on Efficiency

- Consider completely pre-specified adaptive designs with testing adhering to sufficiency principle
    - Differences in operating characteristics due to adaptation rule, not testing method
- Explore efficiency gains over group sequential designs
- Explore efficient types of adaptations
- Compare to frequently proposed adaptation rules

Setting and Notation

- Potential observations X_{Ai} on treatment A and X_{Bi} on treatment B, for $i = 1, 2, ...,$ independently distributed
  - Means μ_A and μ_B and common known variance σ^2
- Parameter of interest: $\theta = \mu_A - \mu_B$
  - Positive values of θ indicate superiority of new treatment
- Up to J interim analyses with sample sizes $N_1, N_2, N_3, ..., N_J$
- At the jth analysis, let
  - Partial Sum: $S_j = \sum_{i=1}^{N_{Aj}} X_{Ai} - \sum_{i=1}^{N_{Bj}} X_{Bi}$
  - MLE: $\hat{\theta}_j = \overline{X}_{Aj} - \overline{X}_{Bj}$

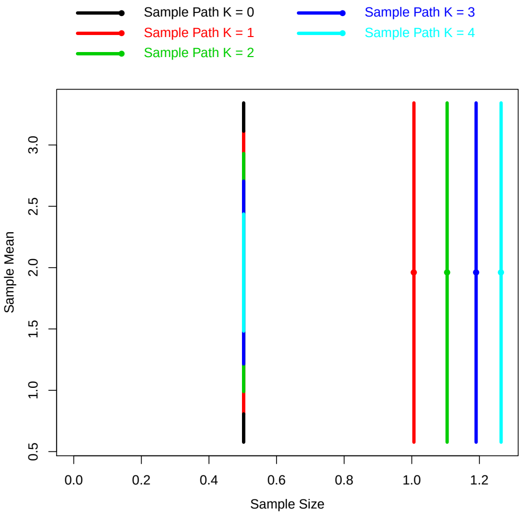
Setting and Notation

- Upper-case letters for random variables, lower-case for fixed quantities
- Use a * to denote incremental data
  - $N_j^* = N_j - N_{j-1}$ (with $N_0 = 0$)
  - $S_j^* = \sum_{i=N_{Aj-1}+1}^{N_{Aj}} X_{Ai} - \sum_{i=N_{Bj-1}+1}^{N_{Bj}} X_{Bi}$
  - $\hat{\theta}_j^* = \overline{X}_{Aj}^* - \overline{X}_{Bj}^*$ and $Z_j^* = \frac{(\hat{\theta}_j^* - \theta_0)}{\sqrt{\frac{\sigma^2}{N_{Aj}^*} + \frac{\sigma^2}{N_{Bj}^*}}}$
- Outcomes immediately observed
- Test null $H_0 : \theta = \theta_0 = 0$ against one-sided alternative $\theta > 0$

A Class of Pre-specified Adaptive Designs

- Single adaptation occurs at analysis time $j = h$
- At adaptation analysis ($j = h$), there are r mutually exclusive continuation sets, denoted C_h^k, $k = 1, \ldots, r$
- Each continuation set C_h^k at adaptation analysis corresponds to future group sequential path k
- Random sample path variable K can take values $0, 1, \ldots, r$
- Define three-dimensional test statistic (M, S, K)
  - M is stage, S is partial sum, K is path at stopping

Example of Adaptive Design



Sampling Density

- $N_j^* = n_j^{k*}$ is fixed conditional on $S_{j-1} = s \in C_{j-1}^k$
- Appealing to the central limit theorem,
  - $S_1^* \sim N(n_1^0\,\theta\,/\,2,\ n_1^0\,\sigma^2)$
  - $S_j^* \mid S_{j-1} \sim N(n_j^{k*}\,\theta\,/\,2,\ n_j^{k*}\,\sigma^2)$

Sampling Density

Following Armitage et al. (1969), density of $(M = j, S = s, K = k)$ is

$$p_{M,S,K}(j,\ s,\ k;\ \theta) = \begin{cases} f_{M,S,K}(j,\ s,\ k;\ \theta) & \text{if } s \in \mathcal{S}_j^k \\ 0 & \text{otherwise} \end{cases}$$

where the (sub)density is recursively defined as

$$f_{M,S,K}(1,\ s,\ 0;\ \theta) \quad = \quad \frac{1}{\sqrt{n_1^0}\,\sigma}\,\phi\left(\frac{s - n_1^0\,\theta\,/\,2}{\sqrt{n_1^0}\,\sigma}\right)$$

$$f_{M,S,K}(j,\ s,\ k;\ \theta) = \int_{C_{j-1}^k} \frac{1}{\sqrt{n_j^{k*}}\,\sigma}\,\phi\left(\frac{s - u - n_j^{k*}\,\theta\,/\,2}{\sqrt{n_j^{k*}}\,\sigma}\right)\ f_{M,S,K}(j-1,\ u,\ k;\theta)\ du$$

for $k = 0, j = 2, \ldots, h$ (if $h > 1$) and $k = 1, \ldots, r, j = h+1, \ldots, J_k$

Sampling Density

Easy to show the following relation:

$$p_{M,S,K}(j,\ s,\ k;\ \theta) = p_{M,S,K}(j,\ s,\ k;\ 0)\exp\left(\frac{s\,\theta}{2\,\sigma^2} - \frac{\theta^2}{2\,\sigma^2}\,n_j^k\right)$$

$\Rightarrow$ MLE is sample mean $\hat{\theta} = \overline{X}_A - \overline{X}_B$

$\Rightarrow$ (N, S) minimally sufficient for θ

Computations

- Can compute density of sample mean, $\beta(\theta)$, ASN(θ), etc.
- All computations just functions of density and/or operating characteristics (OC) of a set of $r+1$ group sequential designs
- Can modify existing group sequential software to carry out computations
- All our results using R package RCTdesign built from S-Plus module S+SeqTrial

Efficiency of Adaptive Testing

Our research on efficiency...

- Define optimality criteria in two simple, realistic RCT settings with different scientific constraints
- Derive optimal competing fixed sample, GS, adaptive designs
  - Restrict attention to symmetric designs
- Compare operating characteristics
- Describe in detail sampling plan of optimal adaptive designs

Setting 1: Optimality Criteria

- Number of analyses constrained to max of two
- Type I error $\alpha = 0.025$, power $\beta = 0.975$ at $\theta = \Delta$
- Initial candidate design: fixed $n = 4\,\frac{(z_{1-\alpha}+z_{\beta})^2}{\Delta^2}$ (WLOG, $\sigma^2 = 1$)
- Primary interest: find most efficient design meeting constraints
  - Efficiency measured by average sample size in presence of truly ineffective (under null) or effective (under alternative) treatment

Setting 1: Optimal GSD

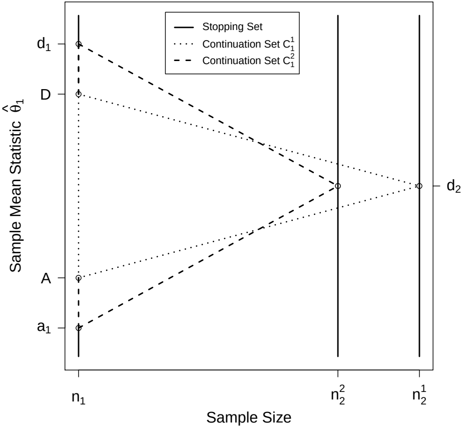
- 2-analysis GSD with Pocock-like stopping boundaries
- Analyses at 50% and 118% of original fixed sample size n
- Stopping boundaries for futility and efficacy at first analysis 0.21Δ and 0.79Δ on sample mean scale
  - $(0.57, 2.21)$ on Z-scale
  - $(4.9\%, 95.1\%)$ on conditional power scale assuming $\theta = \hat{\theta}_1$
  - $(81.8\%, 99.0\%)$ on conditional power scale assuming $\theta = \Delta$
- ASN of 68.54% of fixed sample size n at design alternatives

Finding the “Optimal” Adaptive Design

Find optimal adaptive designs with increasing number r of continuation regions...

1. Holding constant α, β, first-stage stopping bounds of optimal GSD, choose C_1^1 and n_2^1 to minimize ASN at design alternatives based on numerical grid search
2. Proceed to 3 continuation regions by holding C_1^1 constant and finding optimal split of C_1^2 into 2 continuation regions
3. Proceed to 4 continuation regions by optimally splitting $C_1^1 \ldots$

Finding the "Optimal" Adaptive Design



Setting 1: Results

Table: Average, maximal sample sizes of competing designs in units of n

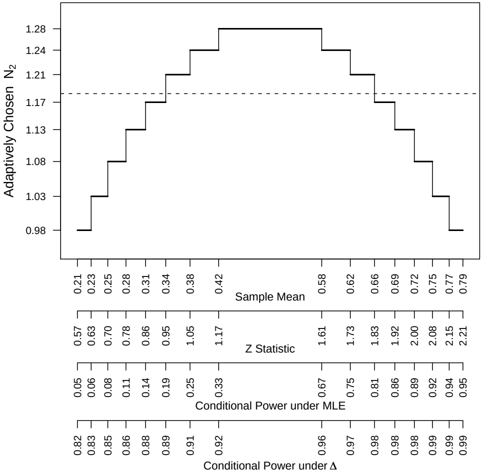
	Number of Continuation Regions								
	0^a	1^b	2	3	4	5	6	7	8
$\text{ASN}_{\theta=0,\Delta}$	1	0.6854	0.6831	0.6828	0.6825	0.6824	0.6824	0.6824	0.6824
% Difference	+45.9%	*Ref*	-0.34%	-0.38%	-0.42%	-0.43%	-0.43%	-0.44%	-0.44%
Maximal N	1	1.18	1.24	1.24	1.26	1.26	1.26	1.26	1.28

a. Fixed Sample Design

b. Group Sequential Design (*Reference* design)

- Efficiency gain by optimal adaptive design minimal ($< 0.5\%$)
- Gain largely achieved with $r = 2$, negligible decreases with $r > 4$

Setting 1: The Optimal Adaptive Design



Setting 1: Describing the Design

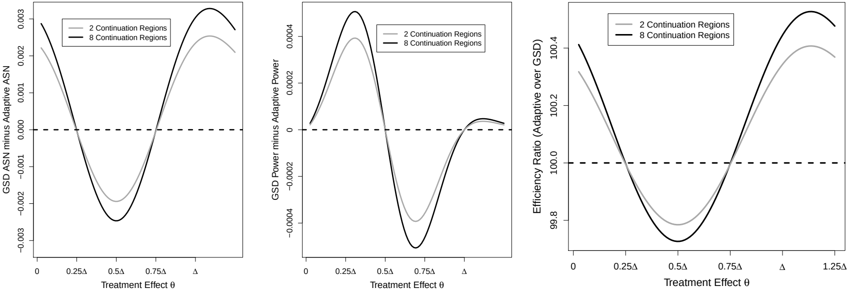
- Increasing # regions only modestly increases maximal N
  - Designs frequently proposed in literature allow $\geq$ 2-fold increase
- Largest maximal sample sizes chosen near center of group sequential continuation region, smallest near boundaries
- $\sim$ Optimal thresholds for increasing N_2 (relative to GSD)
  - $(0.34\Delta, 0.66\Delta)$ on sample mean scale
  - $(0.95, 1.83)$ on Z scale
  - $(0.19, 0.81)$ on CP($z1$; MLE) scale
  - $(0.89, 0.98)$ on CP($z1; \Delta$) scale
- Thresholds on conditional power scale change substantially based on presumption of MLE or Δ as true treatment effect

Setting 1: Other Efficiency Considerations

- Efficiency gain at alternatives ($\theta = 0$ and $\theta = \Delta$) offset by losses at intermediate treatment effects ($0.25\Delta - 0.75\Delta$)
  - ASN increases $\sim$ same magnitude as efficiency gains
- Negligible power differences (< 0.0005) between adaptive design and GSD at intermediate θs
- Adding additional analysis to GSD leads to much larger efficiency gain than allowing adaptivity
  - Reduces ASN of GSD by 6.3% as compared to $< 0.5\%$

Setting 1: Other Efficiency Considerations

- Efficiency index of design A: ratio of fixed sample size needed to match its power over its ASN



Setting 2: Optimality Criteria

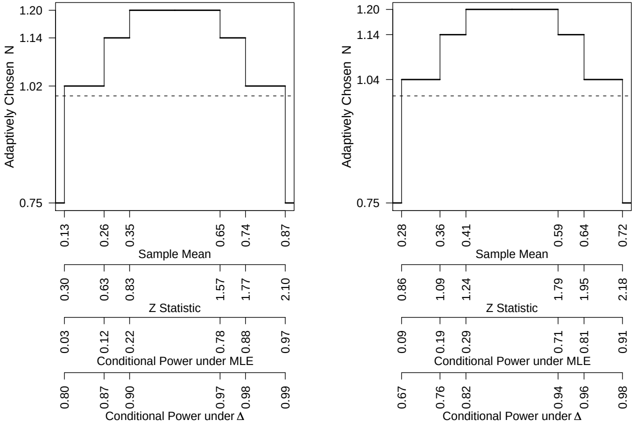
- Only one "stopping analysis"
- Earlier "adaptation" analysis to determine optimal sample size
- $\alpha = 0.025$, $\beta = 0.975$ at $\theta = \Delta$, candidate fixed $n = 4\,\frac{(z_{1-\alpha}+z_\beta)^2}{\Delta^2}$
- Minimum sample size for stopping of $n_{min} < n$ required for adequate safety profile
    - Assume $n_{min} = 0.75n$ (similar patterns with other choices)
- "Adaptation" analysis may occur at range of time points n_{adapt}
    - Let $n_{adapt} = q * n_{min}$ and consider $q \in \{0.1, 0.2, ..., 0.9, 1.0\}$
- Primary interest: find most efficient design meeting constraints

Setting 2: Results

	q (Proportion of n_{min} at which adaptation occurs)									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
ASN$_{\theta=0,\Delta}$	0.99	0.97	0.94	0.91	0.88	0.86	0.84	0.82	0.80	0.78
Maximal N	1.07	1.12	1.16	1.18	1.20	1.21	1.21	1.20	1.18	1.17

- Adding “adaptation” analysis leads to meaningful efficiency gains over fixed sample test, reducing ASN by $\sim$ 20%
- Best design allows stopping at “adaptation” analysis
- Behavior improves as statistical info at adaptation increases

Setting 2: The Optimal Adaptive Designs



(a) q = 0.5

(b) q = 0.8

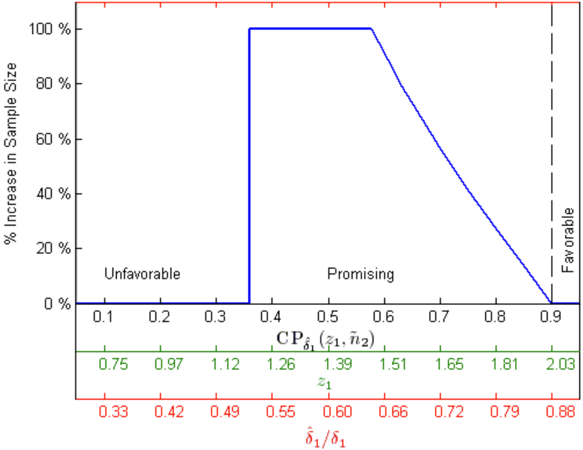
Setting 2: Describing the Designs

- Largest maximal sample size chosen near middle
- N increased up to $\sim 20\%$, much less than frequently proposed
- $\sim$ Optimal thresholds for increasing N ($q = 0.5$)
    - $(0.13\Delta, 0.87\Delta)$ on sample mean scale
    - $(0.30, 2.10)$ on Z scale
    - $(0.03, 0.97)$ on CP($z1$; MLE) scale
    - $(0.80, 0.99)$ on CP($z1$; Δ) scale
- Thresholds on CP scales depend heavily on presumed θ and may not represent intuitive thresholds
- Thresholds on CP($z1$; MLE) scale deviate from designs proposed in literature - have set lower threshold to 36% (MP 2010)

Results on Efficiency

- Optimal adaptive designs attain very small efficiency gains ($< 0.5\%$) over group sequential designs with same # analyses
    - Offset by losses at other plausible treatment effects
    - Far outpaced by adding an analysis to group sequential design
- Insight into good and bad choices of adaptive sampling plans
    - Only few continuation regions and possible final Ns necessary
    - Better to adapt with more information and when stopping permitted
    - Efficient designs qualitatively different than those in literature

Design in Literature (MP 2010)



Limitations

- Many parameters can vary
  - Number, timing of analyses, family of stopping boundaries, definition of “efficiency,” scientific constraints
- We covered fraction of this space
  - Focused on symmetric designs in two settings
  - Defined “efficiency” and “optimal” based on ASN at design alternatives, holding power constant
- True minimum ASN not guaranteed for $r > 2$
  - Sensitivity procedures iterating between adjacent regions do not provide further reduction
- Statistical efficiency not only (or most important) concern...

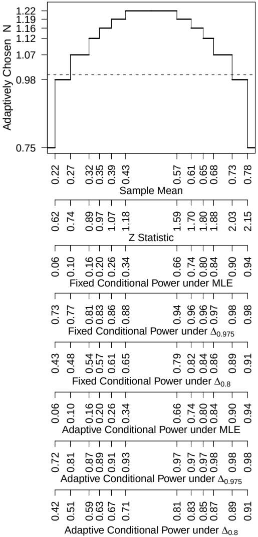
Other Results: Jennison and Turnbull 2006

- Compared optimal pre-specified adaptive designs derived under Bayesian framework to optimal group sequential designs
- Sample size adaptation led to efficiency gains of $< 1.5\%$ (holding constant type I error, power, maximum N, and # analyses)
- "Observed the sampling rules of optimal adaptive tests to be qualitatively different from rules based on conditional power..."
    - Optimal rules selected smaller maximal Ns when interim statistic close to stopping bounds, larger maximal Ns in middle
    - Others reported similar patterns (Posch, Bauer, Brannath 2003)

Efficiency in Survival Setting

- See Emerson, Rudser, and Emerson 2011 (or ask Sarah!)
- In survival setting, statistical information based on # of events, while cost based on # of patients and length of follow-up
- Evaluate tradeoffs between efficiency (average # events), power, cost
- Possibly greater (but still relatively small) benefits from pre-specified adaptation to sampling plan in time-to-event setting
  - Depends on effect size, accrual rate, per-patient cost, interest rate

Stochastic Curtailment and Conditional Power



Stochastic Curtailment and Conditional Power

- Wide range of conditional power values for each boundary as assumptions and reference design vary
  - Efficient threshold on one scale markedly inefficient on another
- Degree of changes in CP do not accurately reflect changes in unconditional power and ASN
- Efficient choices may not correspond to intuitively desirable changes

1-1 Correspondence Between Scales

- 1-1 correspondence between scales for stopping/adaptation boundaries (see Emerson 2007 for relationships)
    - Sample mean, Z statistic, fixed sample P-value, error-spending function, conditional power under $\hat{\theta}$, conditional power under Δ, Bayesian predictive power under some prior, Bayesian posterior probability of some hypothesis
- Choice of scale relatively unimportant if scientific constraints are met, important operating characteristics evaluated
    - Don't choose "intuitive" rule (e.g., stop early if CP$<$ 30%, increase N to achieve CP=90% if CP$<$ 90%) and call it a day!

Collaborate, Evaluate, and Iterate

- Consider scientific/regulatory constraints
  - Maximal feasible sample size, minimal sample size (for adequate safety profile), early conservatism
- Consider important operating characteristics
  - Type I error, power under important alternatives, stopping boundaries on different scales, sample size distribution, stopping probabilities, inference reported at stopping
- Compare candidate designs, modify designs to achieve desired operating characteristics, etc.

Schizophrenia Example (Mehta and Pocock 2010)

- Randomized, phase 3 trial of new drug versus control in patients with negative symptoms schizophrenia
- Primary endpoint: change from baseline in Negative Symptoms Assessment (NSA)
- Desire high power at alternative $\Delta = 2$ with SD ~ 7.5
  - Mean difference as small as 1.6 considered clinically important
- Need complete data on at least 200 patients for adequate safety profile
- Assume overrunning minimal (for ease of illustration)

Schizophrenia Example

- Fixed sample design with $n = 442$ and 80% power at $\Delta = 2$ underpowered at $\Delta = 1.6$
- Fixed sample design with $n = 690$ and 80% power at $\Delta = 1.6$ not feasible
- Also consider group sequential and adaptive designs with up to 2 analyses
    - Compare important operating characteristics

Schizophrenia Software Example

Demonstration of calculations of important operating characteristics in R

1. Statistical Efficiency of Adaptation

2. Complete Inference after Adaptation
    - Inference for Pre-specified Design
    - Inference after Unplanned Adaptation

3. Evaluating Inferential Methods

4. Additional Issues

Motivation for Additional Research

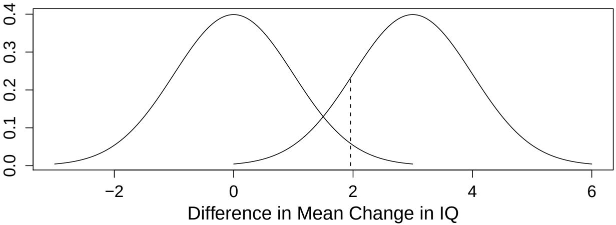
- Despite unclear efficiency gains, adaptive designs implemented in practice, so research needed to propose, evaluate estimation methods
  - Desire for "innovative" designs
  - One sponsor even requires justification if adaptation not included?
- False positive rate and statistical efficiency not only concerns

Case Study: NECAT

- Inhalation of mercury vapor from dental amalgam restorations may have adverse health effects
- Children 6-10 years old randomized to receive dental restoration using either amalgam or resin composite
- Primary outcome: change in full-scale IQ from baseline to 5 years
  - 3 point decline in IQ considered clinically important

Fixed Sample Hypothesis Testing

- Use trial data to decide whether to reject the null hypothesis that amalgam restorations do not lower children's mean IQ
- Design trial to attain low false positive rate (if truly no effect) and high true positive rate (if truly a 3 point average IQ difference)
- Typically 5% false positive rate and 80% or 90% power



Testing versus Estimation

- Testing typically based on *P*-value: probability of obtaining more extreme difference in mean IQ change than what was observed if there were truly no treatment effect
  - If $p < 0.05$, reject null hypothesis of no amalgam effect on IQ
- Four scenarios: What do you conclude?

Study	*P*-value
A	0.263
B	0.263
C	0.025
D	0.025

Testing versus Estimation

- Four scenarios: What do you conclude?

Study	Estimate	Confidence Interval	*P*-value
A	0.5	(-0.4, 1.4)	0.263
B	4.5	(-3.4, 12.3)	0.263
C	0.5	(0.1, 0.9)	0.025
D	4.5	(0.5, 8.4)	0.025

- A: no statistical significance, and ruled out clinical importance
- B: no statistical significance, but consistent with important effect
- C: statistical significance, but ruled out clinical importance
- D: statistical significance, and consistent with important effect

The Need for Good Estimates

- Confirmatory phase III RCTs must produce *interpretable* results
  - Regulatory decisions based on statistical *and clinical* significance
  - Appropriate labeling of newly approved treatment indications
  - Clinicians can effectively practice evidence-based medicine

Complete Inference

Four numbers (with good properties):

- Best point estimate of treatment effect
- Confidence interval providing range of effects consistent with data
- P-value reflecting strength of statistical evidence against no effect

Sequential Analyses: Statistical Challenges

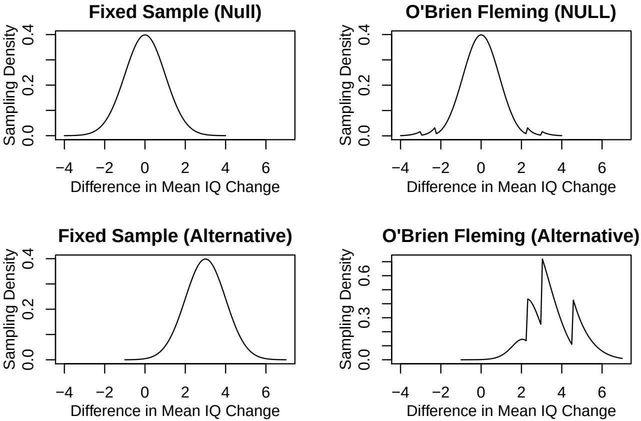
- Sequential testing has implications on estimation of the treatment effect in addition to hypothesis testing
- We stop early only if extreme results are observed
  - Fixed sample estimates such as the sample mean tend to be biased (to the extreme)
  - Confidence intervals do not have correct coverage probabilities (may be conservative or anti-conservative)
- We need point and interval estimates, adjusted for sequential analyses, with desirable "properties"

Connection to Other Types of Studies

- Bottom line: implications of performing *multiple comparisons*
  - Inflated false positive rate
  - Random high bias in estimates of treatment effect for positive results ("winner's curse", "sophomore slump")
- Applies to many other settings
  - Multiple analyses over time
  - Multiple subgroup analyses (e.g. by genetic or other biomarker)
  - Multiple endpoints
  - Publication bias (multiple studies)

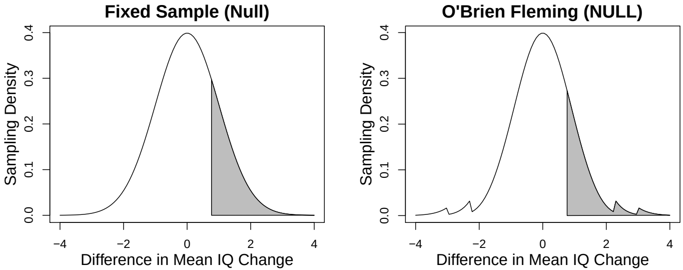
Estimation after Sequential Hypothesis Testing

- Compute estimates, *P*-values based on true sampling density:



Estimation after Sequential Testing

- Example: *P*-values still probability of observing more “extreme” data under null hypothesis of no treatment effect



Well-understood Methods

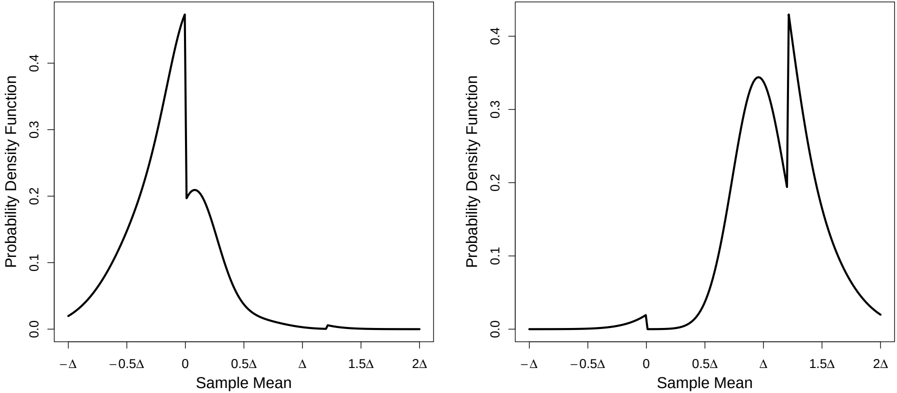
- Extensive literature on estimation after group sequential test
  - Different methods to compute bias-adjusted point estimates, and correct (adjusted) confidence intervals and P-values
  - Extensive evaluation of properties assessing the reliability and precision of estimates, CIs, P-values
  - Variety of software available for design, conduct, analysis of group sequential designs (PEST, East, SeqTrial, SAS, R)
- Adjusted estimates should be reported, but often are not (even by the best journals)

Extension of Group Sequential Approaches

- Extend orderings of outcome space to adaptive setting
  - Compute p-values
  - Compute confidence regions
  - Compute median-unbiased estimates
- Extend bias-adjusted mean to adaptive setting
- Extend software and evaluate methods

Adaptive Sampling Density of Sample Mean

- Under null (left) and alternative (right)



Duality of Testing and Confidence Sets

- Confidence set: all hypothesized values of θ that would not be rejected by appropriately sized hypothesis test given observed data
- Define acceptance region of “non-extreme” results for each θ:

$$A(\theta, \alpha) = \{(j, t, k) : 1 - \alpha \; > \; P[\,(M, T, K) \; \succ \; (j, t, k);\; \theta\,] \; > \; \alpha\}$$

- Use acceptance region to define equal-tailed $(1 - 2\,\alpha) \times 100\%$ confidence set:

$$\mathrm{CS}^{\alpha}(M, T, K) = \{\theta : (M, T, K) \in A(\theta, \alpha)\}$$

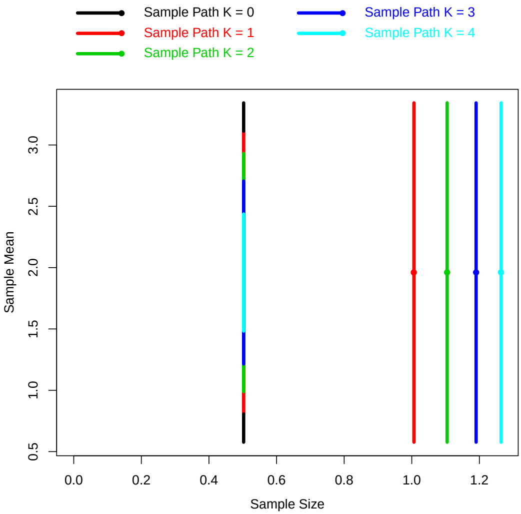
Exact Confidence Sets

To apply, need to define "more extreme" ($\succ$) with outcome ordering:

$$\{(j, t, k) : t \in \mathcal{S}_j^k;\ k = 0, j = 1, \ldots, h \text{ and } k = 1, \ldots, r, j = h + 1, \ldots, J_k\}$$

- Neyman-Pearson: likelihood ratio most powerful for simple hypothesis
- Density does not have monotone likelihood ratio, so composite hypothesis theory for optimal tests and CIs does not apply
- Useful to extend straightforward group sequential orderings and evaluate range of properties under variety of designs
    - Relative behavior likely depends on design and treatment effect

Orderings of Outcome Space



Orderings of Outcome Space

- *Sample mean ordering* (SM). Outcomes ordered according to MLE $T \equiv \hat{\theta}$:

$$(j', t', k') \succ (j, t, k) \text{ if } t' > t$$

- *Signed likelihood ratio ordering* (LR). Outcomes ordered according to signed likelihood ratio test statistic against hypothesized θ':

$$(j', t', k') \succ_{\theta'} (j, t, k) \quad \text{if}$$

$$\text{sign}(t' - \theta') \frac{p_{M,T,K}(j', t', k'; \theta = t')}{p_{M,T,K}(j', t', k'; \theta = \theta')} > \text{sign}(t - \theta') \frac{p_{M,T,K}(j, t, k; \theta = t)}{p_{M,T,K}(j, t, k; \theta = \theta')}, \text{ i.e., if}$$

$$\sqrt{n_{Aj'}^{k'}}(t' - \theta') > \sqrt{n_{Aj}^{k}}(t - \theta')$$

Orderings of Outcome Space

- *Stage-wise orderings*. Outcomes ordered according to "stage" study stops.
    - Earlier is "more extreme"
    - Unlike GS setting, ranks of analysis times and sample sizes not necessarily equal
    - How to rank statistics observed at same stage through different paths?
    - Several ways to impose this in adaptive setting

Stage-wise Orderings

- *Analysis time + Z statistic ordering (Z)*:

$$(j', t', k') \succ (j, t, k) \text{ if } \begin{cases} j' < j \text{ and } t' \in \mathcal{S}_{j'}^{k'(1)} \\ j' > j \text{ and } t \in \mathcal{S}_{j'}^{k'(0)} \\ j' = j \text{ and } z' > z \end{cases}$$

- *Analysis time + re-weighted Z statistic ordering (Z_w)*:

$$(j', t', k') \succ (j, t, k) \text{ if } \begin{cases} j' < j \text{ and } t' \in \mathcal{S}_{j'}^{k'(1)} \\ j' > j \text{ and } t \in \mathcal{S}_{j'}^{k'(0)} \\ j' = j \text{ and } z_w' > z_w \end{cases}$$

- *Statistical information ordering (N)*:

$$(j', t', k') \succ (j, t, k) \text{ if } \begin{cases} n_{j'}^{k'} < n_j^k \text{ and } t' \in \mathcal{S}_{j'}^{k'(1)} \\ n_{j'}^{k'} > n_j^k \text{ and } t \in \mathcal{S}_{j'}^{k'(0)} \\ n_{j'}^{k'} = n_j^k \text{ and } t' > t \end{cases}$$

Point Estimates and P-values

Define the following point estimates for θ given $(M, T, K) = (j, t, k)$:

- *Sample Mean* (MLE): $\hat{\theta} = \overline{X}_A - \overline{X}_B = t$
- *Bias adjusted mean* (BAM) $\check{\theta}$: $E_T[\,T;\, \check{\theta}\,] = t$
- *Median unbiased estimates* (MUE) $\tilde{\theta}_o$: $P[\,(M, T, K) \succ_o (j, t, k);\, \tilde{\theta}_o\,] = \frac{1}{2}$

For $H_0 : \theta = \theta_0$, define a P-value under imposed ordering $O = o$:

- $p\text{-value}_o = P[\,(M, T, K) \succ_o (j, t, k);\, \theta_0\,]$

Statistics as Usual

- We frequently use different orderings of the outcome space in order to carry out tests and compute point, interval estimates
  - Wald vs. Score vs. Likelihood Ratio
- Seek as reliable and precise inference as possible
- Desirable properties in sequential setting enumerated by Emerson, Jennison and Turnbull, and others

Schizophrenia Software Example

Demonstration of calculations in R to compute estimates, confidence intervals, and P-values after fixed, group sequential, and adaptive sampling plans

Interactive Exercise

Interactive exercise to illustrate concepts discussed thus far

1. Statistical Efficiency of Adaptation
2. Complete Inference after Adaptation
   - Inference for Pre-specified Design
   - Inference after Unplanned Adaptation
3. Evaluating Inferential Methods
4. Additional Issues

Unplanned Adaptation: Motivation

- Motivation
    - Flexibility to modify design (e.g., sample size / power) based on external information
        - ★ If truly external (independent), no adjustment to inference needed, but difficult to prove interim data had no role?
    - Flexibility to adapt utilizing information on additional endpoints
- Worth potential losses in reliability, efficiency due to lack of planning?
    - (Plus logistical challenges inherent to all adaptive designs)

Testing versus Estimation

- Many methods to control type I error rate in presence of unplanned adaptation
  - All equivalent to conditional error approach (J+T 2003, Proschan 2009)
- Limited research on estimation after adaptive hypothesis test
  - Exploration of absolute bias of MLE
    - As high as 40% of SD of first-stage sample mean in 2-stage setting (Brannath et al. 2006)
  - Extension of repeated confidence intervals
  - Inversion of conditional error testing approach

Brannath, Mehta, and Posch (BMP) 2009

- Outcomes ordered according to smallest level of significance μ for which a conditional-error based adaptive hypothesis test of $H_0 : \theta = \theta'$ would be rejected:

$$(j', t', k', t_h') \succ_{\theta', GSD} (j, t, k, t_h) \text{ if}$$

$$\mu(j', t', k', t_h'; \theta', GSD) < \mu(j, t, k, t_h; \theta', GSD)$$

- Depends on θ', interim estimate t_h, and original GSD
- But does not depend on what sampling plan we would have chosen had other interim data been observed

Gao, Liu, and Mehta (2012)

- More intuitive derivation of approach to invert conditional error-based tests
- Compute stage-wise ordered p-value of “backward image” of observed test statistic
- Backward image is statistic in outcome space of originally planned design with same stage-wise p-value (conditional on interim estimate) as in adaptively chosen future sampling plan
- Appears to be two-sided generalization of BMP approach

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Assessing Reliability and Precision of Inference

- Confidence sets
  - True intervals
    - ⋆ If $P[\,(M, T, K) \succ_o (j, t, k);\, \theta\,]$ increases in θ for each (j, t, k) (proof found for sample mean ordering)
    - ⋆ Otherwise, negligible effects on coverage
  - Consistency with hypothesis test
    - ⋆ Requires same ordering for decisions, P-values, intervals
  - Shorter expected length

Assessing Reliability and Precision of Inference

- Point estimates
  - Low bias, variance, mean squared error (MSE)
- *P*-values
  - High probabilities of falling below important thresholds
    - e.g., $0.025^2 = 0.000625$ to potentially approximate statistical strength of evidence of two independent studies

Approach to Evaluating Inferential Methods

- Estimates derived in iterative search by numerically integrating several group sequential densities
  - Densities convolutions of normals and truncated normals
  - Difficult to come up with analytic results on relative behavior
  - Resort to Monte Carlo simulation
- Develop extensive comparison framework to evaluate methods
  - 10,000 simulated trials under a range of treatment effects across a variety of adaptive sampling plans

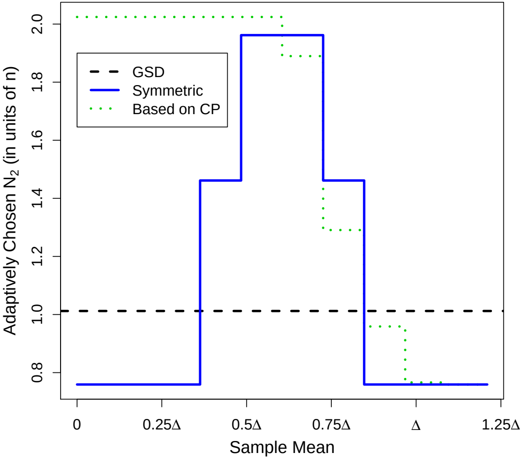
Comparison Framework

Pre-specified adaptive tests of $H_0 : \theta = 0$ against one-sided alternative $\theta > 0$ with $\alpha = 0.025$, power β at $\theta = \Delta$, with varying:

- Degree of early conservatism (reference OF or Pocock GSD)
- Symmetry of early stopping (symmetric or only for superiority)
- Power at Δ (80% to 97.5%)
- Maximum number of analyses (2, 3, or 4)
- Timing of adaptation (25% to 75% of original N_J)
- Maximum allowable sample size (25% to 100% increase)
- Rule for determining final sample size (symmetric or conditional-power based)

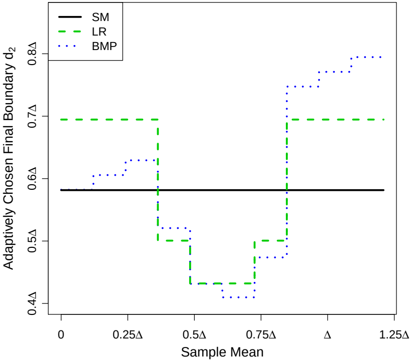
Adaptively Chosen Sample Size

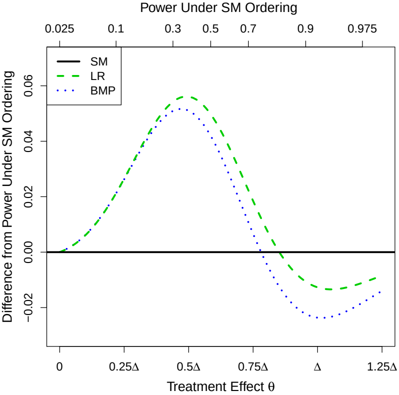
- Example of symmetric and CP-based N_2 functions



Differences in Boundaries and Power

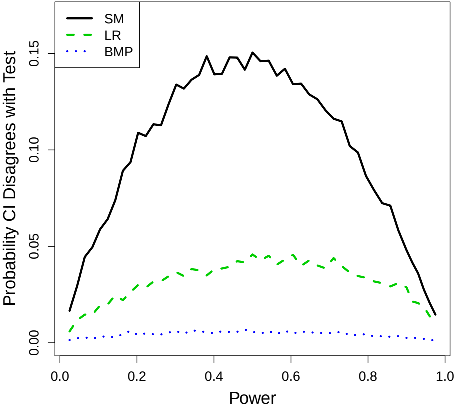
- Comparing testing based on different orderings of outcome space (OF reference, symmetric N_J rule, 100% maximal increase)...





Avoiding Inconsistent Inference

- Should use same ordering for testing as for estimation



Confidence Intervals: Correct Coverage

- Standard error of CI coverage with 10,000 simulations: 0.0022

	OF Reference GSD				Pocock Reference GSD			
Power	Naive	SM	LR	BMP	Naive	SM	LR	BMP
Symmetric N_J function, up to 50% Increase								
0.025	0.9442	0.9455	0.9449	0.9462	0.9425	0.9484	0.9485	0.9481
0.500	0.9314	0.9507	0.9488	0.9507	0.9458	0.9507	0.9504	0.9507
0.900	0.9402	0.9493	0.9478	0.9476	0.9350	0.9465	0.9467	0.9466
CP-based N_J function, up to 100% Increase								
0.025	0.9428	0.9494	0.9497	0.9494	0.9441	0.9502	0.9508	0.9505
0.500	0.9181	0.9462	0.9469	0.9466	0.9355	0.9461	0.9476	0.9462
0.900	0.9291	0.9501	0.9501	0.9501	0.9365	0.9494	0.9489	0.9496

Estimates: Median-unbiased

- SE of probability exceeds MUE with 10,000 simulations: 0.005

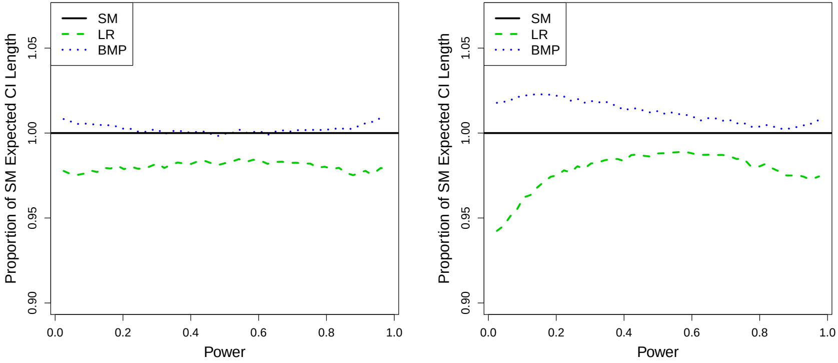
	OF Reference GSD			Pocock Reference GSD		
Power	SM	LR	BMP	SM	LR	BMP
			Symmetric N_J function, up to 100% Increase			
0.0250	0.4956	0.4993	0.4960	0.4983	0.4986	0.4960
0.5000	0.5082	0.5076	0.5081	0.5100	0.5093	0.5095
0.9000	0.5019	0.5006	0.4970	0.5034	0.5028	0.5011
			CP-based N_J function, up to 100% Increase			
0.0250	0.4975	0.4997	0.4958	0.5032	0.5035	0.5025
0.5000	0.5079	0.5075	0.5064	0.5027	0.5027	0.5045
0.9000	0.5001	0.4981	0.5050	0.5105	0.5099	0.5094

Results: Naive Inference

- MLE substantially higher bias than adjusted estimates at all but intermediate effects and higher MSE (up to 40%) across nearly all designs and effects considered
- Naive 95% CIs lack exact coverage, typically 92-93% coverage, occasionally near 90%
- Performance may be worse with more complex multistage designs

Comparing Confidence Intervals: Example

- Reference OF design, symmetric (left) or CP-based (right) N_J function, up to 50% increase, $J = 2$

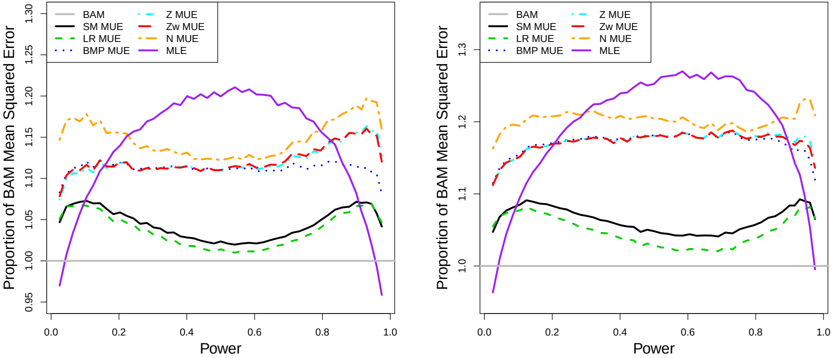


Comparing Confidence Intervals: Trends

- Likelihood ratio ordering shorter expected CI length across nearly all designs and treatment effects studied
  - $\sim 1 - 10\%$ shorter, depending on setting
  - Margin increases with greater potential inflation of N_J
  - Margin slightly larger for CP-based than symmetric N_J function
- Sample mean slightly superior ($\sim 1 - 3\%$) to BMP in some settings, similar in others

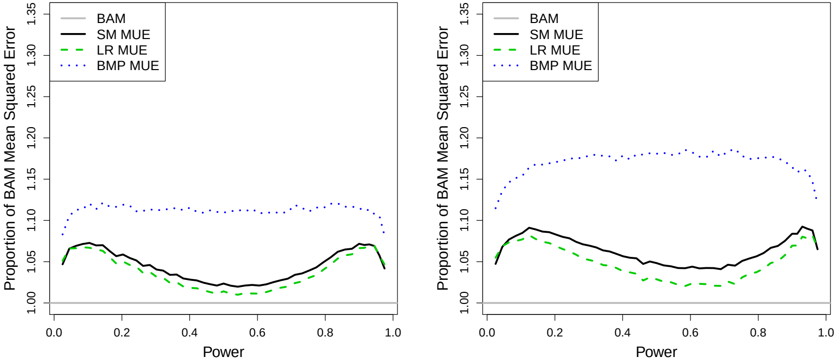
Comparing Point Estimates: Example

- Reference Pocock design, symmetric (left) or CP-based (right) N_J function, up to 100% increase, $J = 2$



Comparing Point Estimates: Example

- Reference Pocock design, symmetric (left) or CP-based (right) N_J function, up to 100% increase, $J = 2$

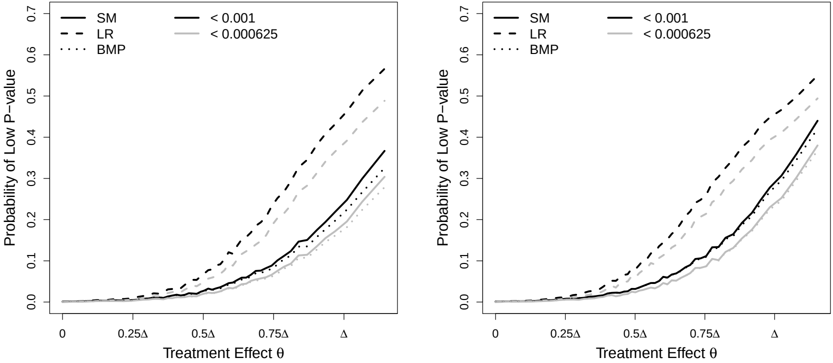


Comparing Point Estimates: Trends

- Bias adjusted mean best MSE across nearly all designs and treatment effects considered
  - $\sim 1 - 20\%$ lower, depending on setting and comparator
  - Margin increases with N_J inflation, CP-based adaptation
  - Lower bias at extreme effects, variance at intermediate effects
  - All CIs observed to always contain BAM
- SM, LR MUEs up to 15% lower MSE than BMP MUE
- LR MUE slightly superior ($\sim 1 - 3\%$) to SM MUE in some settings, similar in others

Comparing *P*-values: Example

- Reference OF (left) or Pocock (right) design, CP-based N_J function, up to 50% increase, $J = 2$



Comparing *P*-values: Trends

- Likelihood ratio ordering tends to demonstrate greater probabilities of potentially “pivotal” *P*-values
  - Up to $\sim 20\%$ greater (on absolute scale), depending on setting
  - Margin increases with greater N_J inflation, CP-based adaptation
  - Margin larger for tests derived from OF reference designs
- Sample mean modestly superior (up to $\sim 10\%$ on absolute scale) to BMP in most settings, similar in others

Summary and Conclusions

- Bias adjusted mean most reliable and precise point estimate
- Likelihood ratio ordering CIs and P-values behaved best
- Margins increase with N_J inflation, CP-based N_J function
- Qualitative differences persist varying many design parameters
    - Quantitative differences decrease for early, late adaptations
- MLE and inference using other orderings poor relative behavior

Cost of Planning not to Plan

- Most proposed adaptations could be pre-specified at design stage
- Substantial cost of failing to plan ahead and resorting to conditional error-based (BMP) estimation
  - Large increase (up to 20%) in MSE of point estimate
  - Modest increase (up to 10%) in expected CI length
  - Large decrease (up to 20%) in probability of pivotal P-value
  - Cost is largest for typically proposed adaptation rules
  - Due to inversion of conditional error tests or stage-wise ordering of backward image?
- BMP inference has reasonable behavior if needed

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Case Study: An Antidepressant in MDD

- Randomized placebo-controlled clinical trial to study safety and effectiveness of novel antidepressant in major depressive disorder
- Primary outcome is 50% improvement at 8 weeks in Hamilton depression rating scale
- 30% response rate expected on placebo
- 10% improvement on treatment considered minimal clinically important difference

Case Study: An Antidepressant in MDD

Candidate designs:

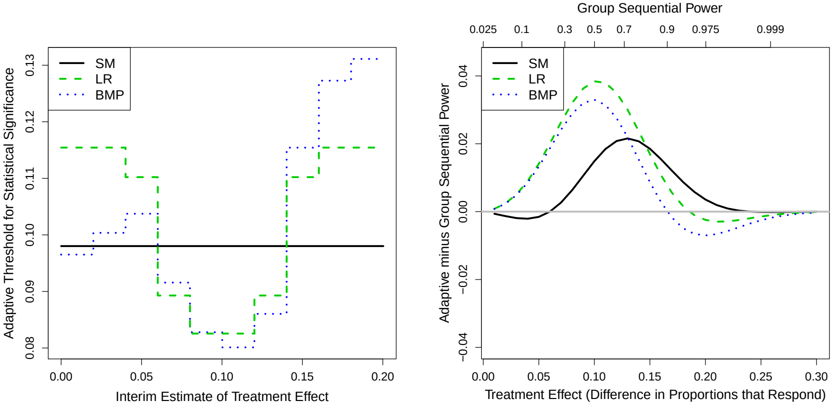
- Fixed sample design with 176 participants per arm
  - $\alpha = 2.5\%$ type I error, $\beta = 90\%$ power at $\theta = 0.165$, threshold for statistical significance of 10%
- Two-analysis O'Brien and Fleming and Pocock group sequential designs with same α, β, significance threshold
- Adaptive designs derived from these GSDs, using symmetric or conditional power-based rules

Statistical *versus* Clinical Significance

- Goal of RCTs not statistical significance but instead "statistically reliable evaluation regarding whether the experimental intervention is safe and provides clinically meaningful benefit." (Fleming 2006)
- Yet adaptation often proposed to increase conditional power presuming treatment effects below the MCID
- Threshold for statistical significance on scale of estimated treatment effect varies greatly under LR, BMP orderings
    - May fall below MCID: ranges from 8.0% to 13.2%

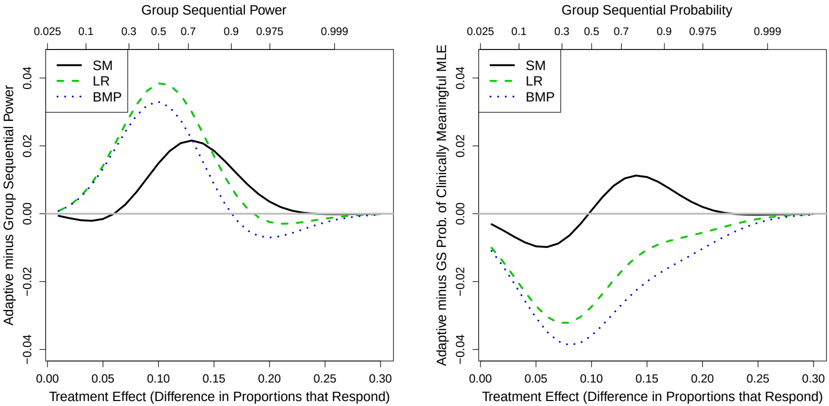
Statistical *versus* Clinical Significance

- Boundary differences result in power differences (OF reference, symmetric N_J rule, 50% maximal increase)...



Statistical *versus* Clinical Significance

- Consider success as statistical *and clinical* ($>$ 10%) significance:



Maintaining Confidentiality

- Maintaining confidentiality protects trial integrity
- Additional challenges in conduct of adaptive trial
  - Sample size may be function of interim estimate:

$$N_2(\hat{\theta}_1) = \left(\frac{ \frac{d_2^0 \, n_2^0 - \hat{\theta}_1 \, n_1}{\sqrt{n_2^0 - n_1}} - \sqrt{V} \, \Phi^{-1}(0.1) }{ \hat{\theta}_1 } \right)^2 + n_1$$

  - Potential unblinding through new recruitment targets
    - ★ Example: New $N_2 = 227$ allows approximation of 13% estimate
  - Less likely with only few possible final sample sizes

Maintaining Confidentiality

Possible approaches if knowledge of adaptively chosen sample size and adaptation rule allows reasonably precise estimate of interim effect?

- Blind trial investigators involved in treatment, outcome assessment to new sample size
- Blind trial investigators to Adaptive Charter (which describes adaptation rule)
- Rely on unplanned adaptation by DMC
  - Too much to ask of DMC? Will require sponsor input/knowledge regardless...

Logistical and Ethical Issues

- Increased effort in planning, protocol development, monitoring
  - FDA Draft Guidance: “added complexities... call for more detailed documentation”
  - SAP must include “summary of each adaptation and its impact upon critical statistical issues”
- Ethics of weighting subjects differently
  - And should weighted or unweighted estimate be reported?
- Allow even greater bias knowing crude estimates will be reported in journals/labeling, interpreted as reliable

Additional Challenges: Summary

- Relative behavior of LR, BMP orderings, adaptive designs in general suffer when considering statistical *and clinical* significance
- Important added logistical and ethical challenges in design and conduct
- In many cases, these considerations alone may render adaptive design inappropriate

Summary and Conclusions

- Pre-specified adaptation attains minor efficiency gain ($< 0.5\%$)
    - Efficient designs differ qualitatively from those in literature
    - Should evaluate important operating characteristics and modifying/comparing candidate designs
- Estimation methods after adaptive test developed and evaluated
    - Avoid using naive CIs and MLE
    - Bias adjusted mean, LR or SM ordering better behavior with respect to important measures of reliability, precision
    - Failing to pre-specify (BMP) comes with meaningful cost

Editorial

- Carefully compare candidate designs before deciding to adapt
- Potential gains in flexibility, efficiency through sample size adaptation likely not worth added interpretability, logistical challenges in most settings
- Possibly more promise with adaptive subgroup selection (e.g., with a pre-specified, clearly defined targeted subset expected to benefit more – see Rosenblum research)

Thank you