Module 2. Introduction to Adaptive Designs, and Skeptics' Points of View

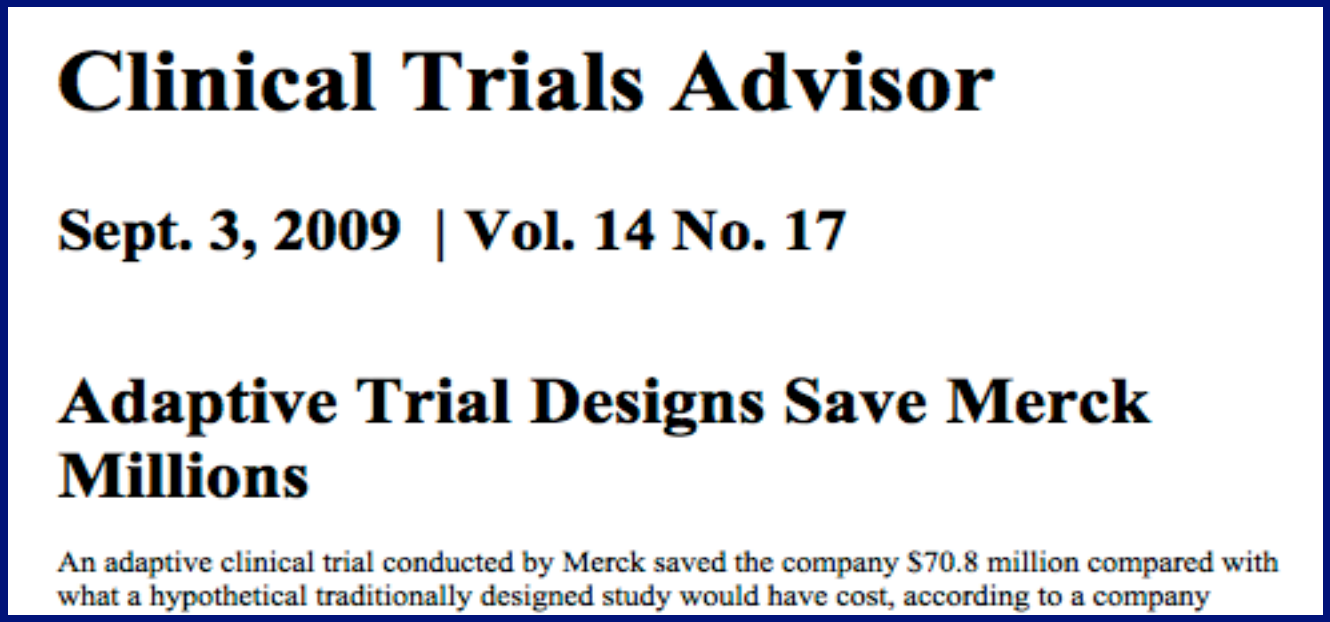
Adaptive Clinical Trial Designs

FDA is Interested:

"A large effort has been under way at FDA during the past several years to encourage the development and use of new trial designs, including enrichment designs."

Adaptive Clinical Trial Designs

- Pharmaceutical Companies are Interested:



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Adaptive Trial Designs Save Merck Millions

An adaptive clinical trial conducted by Merck saved the company $70.8 million compared with what a hypothetical traditionally designed study would have cost, according to a company

"An adaptive clinical trial conducted by Merck saved the company $70.8 million compared with what a hypothetical traditionally designed study would have cost…"

Why Use Adaptive Designs?

Benefits:

- Can Give More Power to Confirm Effective Drugs and Determine Subpopulations who Benefit Most
- Can Reduce Cost, Duration, and Number of Subjects of Trials

Designs Must:

- Guarantee Correct Probability of False Positive Results (e.g. 0.05)
- Lead to Interpretable Results

Goals of this part of course

- Give an overview of adaptive randomized trial designs.
- Present ideas from FDA draft guidance on adaptive designs for drugs and biologics
- Discuss the advantages, limitations, and open problems for various types of adaptation.
- Brief overview of group sequential designs

Themes

- Prespecify Decision Rules for Making Adaptations
- Tradeoff between Flexibility and Power
- Tradeoff between Power, Sample Size, Number of Patients in Inferior Arm
- Perspective of FDA, pharma company, subject in a trial

Group Sequential Randomized Trial Designs

- Participants Enrolled over Time
- At Interim Points, Can Change Sampling in Response to Accrued Data:
  - Standard group seq. design: Can Stop Trial Early, e.g. for Efficacy, Futility, or Safety
  - Adaptive: Can Change Probability of Assignment to Different Arms (e.g. to Maximize # Patients Assigned to Best Arm)
  - Can Recruit from Subpopulation in which Treatment Effect is Strongest ("Enrichment")

Enrichment Design Example

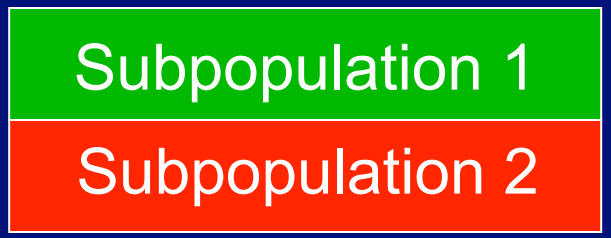
Population: Lung cancer patients with metastasis. Some are eligible for existing therapy, some are not.

Research Questions: Does addition of a new therapy improve mean outcome for total population? For those who are not eligible for existing therapy?

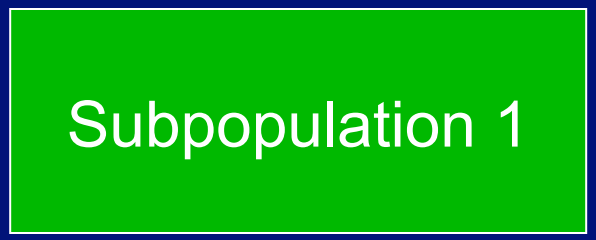
Prior Data Indicates: Treatment effect greatest for those not eligible for existing therapy.

Some Possible Fixed Designs

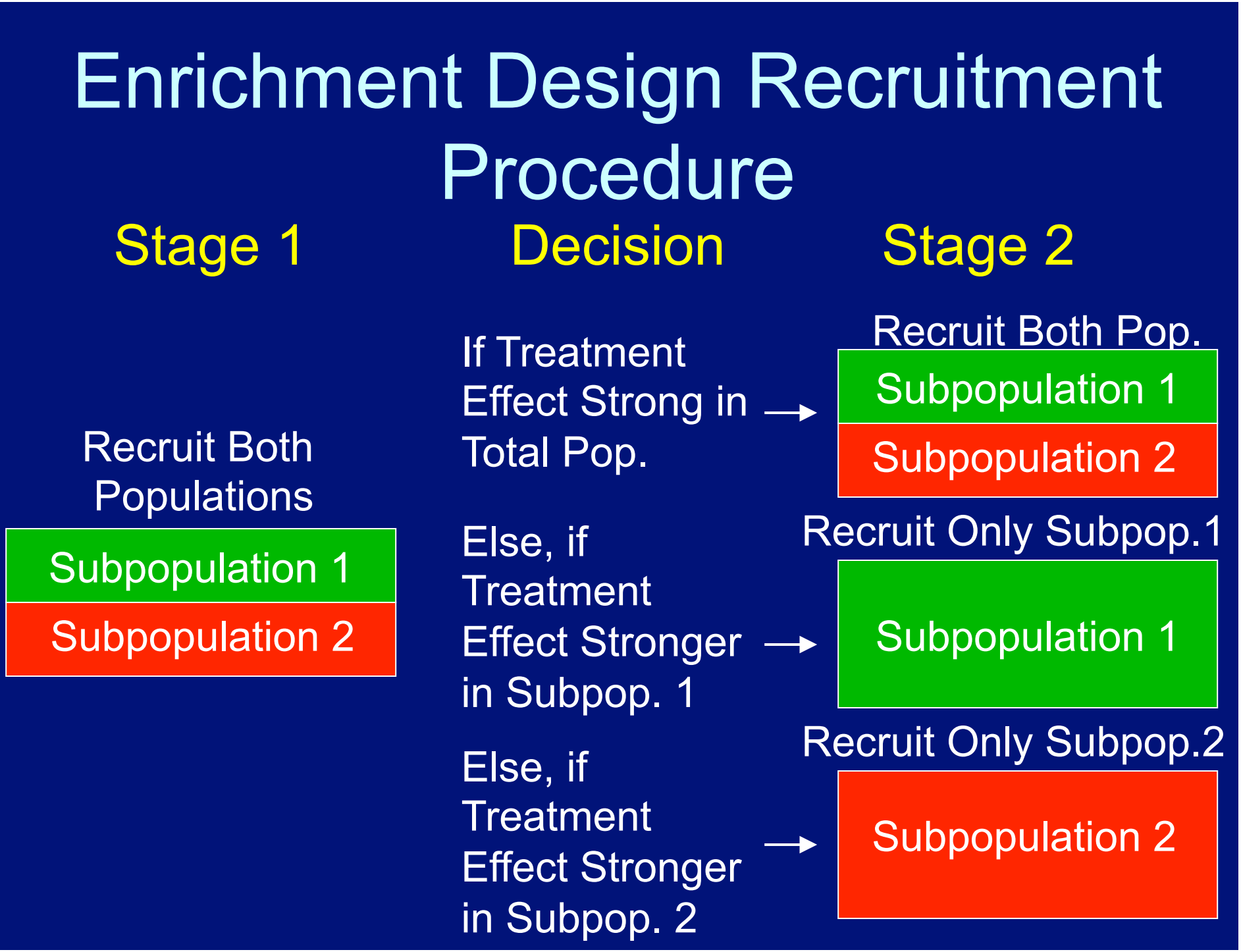
- Enroll from total population (both those eligible for existing treatment and those not)



- Enroll only from those not eligible for existing treatment



Enrichment Design Recruitment Procedure



FDA Critical Path Opportunities

"Advancing Innovative Trial Designs"

34. Design of Active Controlled Trials.

35. Enrichment Designs. If biomarkers can reliably identify individuals with a high probability of response to a therapy, trials could focus on such patients.

FDA Critical Path Opportunities

36. Use of Prior Experience or Accumulated Information in Trial Design.

"Consensus and clarification is needed on questions such as:

- When can extra trial arms be dropped?
- When can an early marker be used to choose which treatment to carry forward or to choose a subset for analysis?

FDA Critical Path Opportunities

"Consensus and clarification is needed on questions such as: (con't)

- When is it valid to modify randomization based on results, for example, in a combined phase 2/3 cancer trial?
- When is it valid and under what situations can one stage or phase of a study be combined with the second stage or phase?

Fleming (2006)

- Fleming (2006) Standard versus adaptive monitoring procedures: A commentary
- Issues:
  - Efficiency
  - Interpretability
  - Reliability of Interim Results
  - Leaking Information
  - Ethical Concerns

Below, I give key arguments, and some of my own thoughts.

Fleming (2006)

Issue of Efficiency:

Some adaptive sample size adjustment methods are inefficient, as they don't use sufficient statistics.

For example, Cui et al. (1999) method allows arbitrary change to sample size after interim analysis, but fixed weights on each stage's Z statistics.

E.g. final Z-statistic = $(Z_1+Z_2)/\sqrt{2}$.

Fleming (2006)

Issue of Efficiency:

Some adaptive sample size adjustment methods are inefficient, as they don't use sufficient statistics.

However, some designs, e.g. response adaptive randomization that targets Neyman allocation, are more efficient than non-adaptive design. We also discuss adaptive enrichment designs that cannot be dominated by standard designs.

Fleming (2006)

Issue of Interpretability:

Estimates of treatment effect will be biased if e.g. stop early.

This is also an issue for standard group sequential designs. But there is a worry it may be worse for adaptive designs. We consider this later in course when we discuss confidence intervals.

Fleming (2006)

Issue of Reliability of Interim Results:

May be misled into making a poor adaptation decision by highly variable early results (due to low sample size at interim analysis).

It's important that adaptive trials only make major changes when reliable information is available.

Fleming (2006)

Issue of Leaking Information:

Prejudgment of unreliable results based on limited data “could adversely impact patient accrual, continued adherence to trial regimens, and ability to obtain unbiased and complete assessment of trial outcome measures.”

Fleming (2006)

Ethical Issues:

Will patients understand risks/benefits in complex design?

Wittes and Lachenbruch (2006)

Discussion: Opening the Adaptive Toolbox.
Issues:

- Adaptive designs may be used as excuse to be lazy in planning a trial.
-Adapting based only on nuisance parameters.
-Internal vs. external information.

Wittes and Lachenbruch (2006)

Issue that adaptive designs may be used as excuse to be lazy in planning a trial.

Companies may want to fund small trial, and then extend if it looks promising (since can argue for e.g. more venture capital money).

Could lead to sample size larger than a well-planned fixed trial (inefficiency).

Wittes and Lachenbruch (2006)

Issue of adapting based only on nuisance parameters.

Certain nuisance parameters, such as the variance for continuous outcomes, can be used to calibrate sample size without fear of inflated type I error.

Wittes and Lachenbruch (2006)

Issue of internal vs. external information.

Can make adaptation based on external information (e.g. results from a separate trial) without fear of increased Type I error.

References

Fleming, Thomas R. "Standard versus adaptive monitoring procedures: a commentary." Statistics in medicine 25.19 (2006): 3305-3312.

Wittes, Janet, and Peter A. Lachenbruch. "Opening the adaptive toolbox." Biometrical journal 48.4 (2006): 598-603.

FDA Draft Guidance on Adaptive Designs for Drugs and Biologics (2010)

- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf

FDA Draft Guidance on Adaptive Designs

Focus is AW&C (adequate and well-controlled) trials.

Distinguishes well understood vs. less well understood adaptations.

Explains chief concerns: Type I error, bias, interpretability.
It is very well written, thoughtful, and accessible document.

FDA Draft Guidance on Adaptive Designs

Well Understood Adaptations:

- **Adapt Study Eligibility Criteria Using Only Pre-randomization data.**
- **Adapt to Maintain Study Power Based on Blinded Interim Analyses of Aggregate Data (or Based on Data Unrelated to Outcome).**
- **Adaptations Not Dependent on Within Study, Between-Group Outcome Differences**

FDA Draft Guidance on Adaptive Designs

Well Understood Adaptations:

- **Group Sequential Methods (i.e. Early Stopping)**

FDA Draft Guidance on Adaptive Designs

Less-Well Understood Adaptations:

- **Adaptive Dose Selection**
- **Response-Adaptive Randomization**
- **Sample Size Adaptation Based on Interim-Effect Size Estimates**
- **Adaptation of Patient Population Based on Treatment-Effect Estimates**
- **Adaptive Endpoint Selection**

FDA Draft Guidance on Adaptive Designs

Adaptive Dose Selection

Dropping Doses (Arms).

Use of biomarker for dose selection.

[Need statistical adjustment.]

FDA Draft Guidance on Adaptive Designs

Response Adaptive Randomization

Population being enrolled may change over time (e.g. more events observed).

This could cause inflated Type I error and bias.

FDA Draft Guidance on Adaptive Designs

Adaptation of Patient Population Based on Treatment-Effect Estimates

"These designs are less well understood, pose challenges in avoiding introduction of bias, and generally call for statistical adjustment to avoid increasing the Type I error rate."

FDA Draft Guidance on Adaptive Designs

Guide to reporting simulations (pp. 38-39):

Investigate Type I error, power, bias, under variety of data generating distributions.

Compare to fixed designs.

Not sufficient to show Type I error controlled via simulations.

Interesting question: what is best time to do adaptations? Early vs. later?

Overview of Standard Group Sequential Testing

Sequential Design, Adaptive Sample Size

Overview

Advantages: May be able to stop early if strong signal of treatment effect.

Can ensure adequate power by accruing enough data before doing hypothesis test.

Interim analysis times can be function of "information" accrued.

Disadvantage: If don't stop early, need more subjects than in equivalent trial with no early stopping allowed. Biased estimates.

Group Sequential Testing (Early Stopping)

At prespecified interim analyses, do a test, and possibly stop the trial for efficacy or futility.

Advantage: May be able to stop early if strong signal of treatment effect. Interim analysis times can be function of "information" accrued.

Disadvantage: If don't stop early, need more subjects than in equivalent trial with no early stopping allowed. Biased estimates.

Simple Example: Static Design

[From Jennison and Turnbull (2000), Ch.2]

Two arm trial, ½, ½ randomization.

Responses are $N(\mu_T,\sigma^2)$, $N(\mu_C,\sigma^2)$.

Null Hypothesis: $\mu_T=\mu_C$.

Want Type I Error at most 0.05.

Want Power = 0.9 at alternative: $\mu_T-\mu_C=1$.

Assume $\sigma^2=4$. Then need in each arm:

$$n \approx 2 \times 4 \times \frac{[\Phi^{-1}(0.975) + \Phi^{-1}(0.9)]^2}{[1-0]^2} = 84.1$$

Simple Example: Seq. Design using Pocock Boundaries

At interim analyses, stop and reject null if Z-statistic exceeds Pocock cutoffs.

Consider 5 equally spaced interim analyses.

Cutoff is 2.41 at all interim analyses.

(Had it been 1.96, Type I error would be 0.14.)

What is max. sample size needed?

102 (> 84).

Pocock Stopping Boundaries

At alpha = 0.05, 2-sided, Z-statistic cutoffs:

Number Analyses	Pocock Boundary
1	1.96
2	2.18
3	2.29
5	2.41
10	2.56

Simple Example: Seq. Design, O'Brien-Fleming Boundaries

At interim analyses, stop and reject null if Z-statistic exceeds O'Brien-Fl. cutoffs.

Consider 5 equally spaced interim analyses.

Cutoffs are 4.56, 3.23, 2.63, 2.28, 2.04.

What is max. sample size needed?

86 (> 84).

O'Brien-Fleming Stopping Boundaries

At alpha = 0.05, 2-sided, Z-statistic cutoffs

Number Analyses	O'Brien Fleming Boundaries
1	1.96
2	2.80, 1.98
3	3.47, 2.45, 2.00
5	4.56, 3.23, 2.63, 2.28, 2.04

Max. Sample Size vs. Static Design

How much is max. sample size "inflated" in sequential testing vs. fixed design? R:

Number Interim Analyses	Pocock boundar.	O'Brien-Fleming
1	1	1
2	1.100	1.007
3	1.151	1.016
5	1.207	1.026

Expected Sample Size vs. Static Design

How does Expected Sample Size in sequential testing compare to fixed design, at alternat.?

Number Interim Analyses	Pocock boundar.	O'Brien-Fleming
1	1	1
2	0.78	0.85
3	0.72	0.80
5	0.69	0.75

Expected Sample Size vs. Static Design

How does Expected Sample Size in sequential testing compare to fixed design, at null.?

Number Interim Analyses	Pocock boundar.	O'Brien-Fleming
1	1	1
2	1.08	1.01
3	1.13	1.01
5	1.18	1.02

Pocock vs. O'Brien-Fleming

Pocock more aggressive earlier, but larger max. sample size, and larger sample size variability. Better when true treatment effect relatively large, but worse otherwise.

Consider treatment of rare disease, subjects enter study at 40/year. Max duration is:

4.25 years for static design

4.5 years for O'Brien-Fleming

5.25 years for Pocock

Flexible Single Testing Time based on Information Accrued

Prespecify that trial will continue until a certain information level (I_{max}) is achieved, at which time a test will take place.

$$I_{\max} = \frac{[\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta)]^2}{[\psi_{alt} - \psi_0]^2} = n_{final}/\sigma^2.$$

Type I error (asymptotically) controlled.

Flexible Interim Analysis Times based on Information Accrued

Interim analysis times based on information accrued I(n).

E.g., if outcome binary:

$$I(n) = \frac{1}{Var_n(\hat{p}_A - \hat{p}_B)} \approx \frac{n}{\hat{p}_n(1-\hat{p}_n)}.$$

Interim analysis when information equals: e.g. ½ of

$$I_{\max} = R\frac{[\Phi^{-1}(1-\alpha)+\Phi^{-1}(1-\beta)]^2}{[\psi_{alt}-\psi_0]^2}.$$

Adapting Randomization Probabilities

Adapting Randomization Probabilities

Q: Why adapt the randomization probabilities?

A: To get more power and precision.

Adapting Randomization Probabilities

Q: How does adapting rand. Probabilities (potentially) give more power and precision?

A:

1. Improving balance on prognostic covariates (Covariate-adaptive designs)
2. Assigning more subjects to arm with greater variance in outcome (Response-adaptive designs)

Covariate Adaptive Designs

Methods to improve balance of prognostic covariates (compared to simple randomization):

1. Block randomization
2. Block randomization stratified by prognostic covariates
3. Biased-coin designs (bias randomization prob. of future subjects to correct observed imbalance)
4. Minimization (of a measure of imbalance)

Adapting Randomization Probabilities

Block randomization:

E.g. in blocks of 4 envelopes, with 2 “treatment” envelopes and 2 “control” envelopes. Overall balance can be off by at most 2!

Block randomization stratified by prognostic covariates

E.g. blocks of 4 envelopes for each stratum of prognostic covariates.

Balance in each stratum off by ≤ 2.

Adapting Randomization Probabilities

Biased coin:

Idea is to select randomization probability for each subject "biasing" toward balance.

E.g. Efron's biased coin: if more than ½ of subjects so far are in treatment group, then next subject gets prob. $p > ½$ of being in control group, and vice versa.

If $p = 1$, then this is example of minimization.

Adapting Randomization Probabilities

Biased coin designs for covariate adaptation:

1. Zelen's model: if imbalance in next subject's covariate stratum > 2, then deterministically assign to improve balance. Else assign with p = 1/2.
2. Pocock-Simon model: based on weighted combination of imbalances in each covariate stratum (with bigger weight for more important covariates), use p-biased coin to improve balance.

Adapting Rand. Probabilities

Friedman-Wei urn:

Wei's urn model: start with urn having

k red (treatment) and k white (control) balls. Draw one and assign to that arm, and replace it and also add b balls of opposite color. Repeat.

For covariate adaptation:

One urn for each covariate value. Draw from most unbalanced urn as above, and now add b opposite balls to each urn corresponding to that subject's covariate values.

Response Adaptive Randomization

Play the winner rules:

Deterministic version: if last patient outcome is “success,” assign that treatment again; else assign other treatment.

Randomized version:

Use an urn of course! Draw from urn for treatment assignment. If got treatment A and “success,” then add b Type A balls; else add b type B balls.

Response Adaptive Randomization

Play the winner rules:

Randomized version:

Use an urn of course! Draw from urn for treatment assignment. If got treatment A and "success," then add b Type A balls; else add b type B balls.

Properties: ratio of number assigned to A vs. B converges to $(1-p_B) / (1-p_A)$, for p_A, p_B the success probabilities.

Response Adaptive Randomization

Neyman Allocation:

How should allocation be done to get most power at a given sample size, when the final estimator/test based on estimated risk difference?

Intuitively, want to assign more subjects to arm with larger variance. Neyman allocation:

$$n_A / n_B = \sqrt{\frac{p_A q_A}{p_B q_B}}.$$

Response Adaptive Randomization

Where does Neyman allocation come from?

Asymptotic variance of empirical risk difference: $\frac{p_A q_A}{n_A} + \frac{p_B q_B}{n_B}$.

To minimize it subject to total sample size = n: $n_A + n_B = n$,

use simple calculus to get: $n_A / n_B = \sqrt{\frac{p_A q_A}{p_B q_B}}$.

Response Adaptive Randomization

"Ethical" allocations:

How should allocation be done to minimize expected number of failures subject to power constraint?

Intuitively, want to assign more to arm with larger success probability.

"Ethical" allocation:

$$n_A / n_B = \sqrt{\frac{p_A}{p_B}}.$$