Methods for Incorporating Flexibility in Clinical Trials

Janet Wittes
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Statistics Collaborative

Option #1: Do as planned

- Design a study
  - Unambiguous protocol
  - Rigorous analysis plan
- No interim peeking at the data
- Complete the protocol as planned
- Analyze the data as planned

Goals of flexible designs

- Prevent harm to participants
- Increase probability of assigning the best treatment to the participants in the trial
- Speed drug development
- Find right answer faster than a fixed design
- Get scientifically more correct results

Little vs. big changes

- Little
  - Clarifying protocol
  - Administrative changes
- Big: need approval
  - IRBs
  - Inform or reconsent participants
- Very big: change design

Prespecification

- Highly desirable
- Not sufficient
- Not necessary

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Rigor vs. rigidity

Not sufficient- stepwise not alpha-preserving

Step 1. ANOVA will assess effects of X & Y. If p-value for Rx × X or Y is <0.15, the data will be pooled appropriately.

Step 2. After pooling, use ANOVA to test Ho.

Not sufficient- language ambiguous

The primary efficacy endpoint will be analyzed by survival methods such as the log-rank test.

Not sufficient-structurally biased

1. The primary analysis will be performed in the

per protocol population.

2. Cases will be counted

if they occur > 14 days after the 3rd dose of vaccine.

Not necessary

- But this is not a license to do whatever!
- Design carefully!!
- Don’t intend to make unplanned changes!!!

Nature of change

- Structured
- Unacceptable
- Unstructured, but acceptable
- Unstructured, but nearly acceptable

Who makes changes?

- Blinded: Sponsor & investigators
- Unblinded: DSMB

Structured

- Interim analysis -DSMB
  - Safety
  - Efficacy
  - Futility
- Sample size recalculation
  - Unblinded: DSMB
  - Blinded: Sponsor/investigators

Sample size recalculation

- Nuisance parameters
- Effect size
  - Don’t use methods to save sample size
  - Blinding may be difficult
  - New effect size may not be of interest

Unacceptable

- Betting on the horse after the race
- Finding the subgroup
- Censoring at crossover
- Ambiguous analysis plan
  - “such as”
  - “some covariates”

Unstructured but acceptable

- Modifying entry criteria if not for efficacy
- Changing analysis of primary endpoint
- Changing primary endpoint

Defining primary endpoint
Example: Post-CABG

- Aggressive lipid lowering post CABG
- Angiographic endpoint
- Design
  - Randomize
  - Take angiogram
  - Wait five years
- Endpoint????

Why was post-CABG ok?

- Blind for five years
- Sized on simple endpoint
- We knew we could do better
- Final endpoint: correlated binary

Expanding endpoint: large coronary disease trial

- Clinical endpoints
  - CV death
  - MI
  - Urgent revascularization
- Endpoint rate too low
  - Added additional endpoints
  - Proustian question: how to recapture the past

Changing endpoint: muscle wasting disease

- Two competing primaries - endurance
  - 6 m walk
  - 3 m stair – also assesses respiratory function
- Chose stair climb
- During trial, saw people reached top
- Changed to walk distance

Changing analysis: lung trial

- Endpoint: 6 month FEV_1
- Protocol:
  - ANOVA at 6 mo
  - FEV_1 as baseline covariate
- Data analysis plan
  - Longitudinal analysis
  - Final test: contrast at 6 mo
- Preserves spirit, not letter, of protocol

Third line cancer trials

- Primary endpoint: mortality
- Secondaries: TTP, PFS, etc.
- Strategy #1:
  - Size for mortality
  - If you lose, argue for PFS
- Strategy #2
  - Co-primary
  - Split alpha between mortality and PFS

The gamble

- Strategy #1: FDA etc. may not agree
- Strategy #2: Sample size increases

Consequence to sample size

$$\{(z_{1-\alpha/2}+z_{\beta})/(z_{1-\alpha/4}+z_{\beta})\}^2$$

- Splitting alpha at 0.025/0.025 increases sample size ~ 20% for trials powered at 80 –90%

Unstructured, but nearly acceptable –cancer example

- Independent review of response
- Protocol says: no clinical input
- Fails to distinguish cancer from cyst
- Conclusion: add clinical input (but remain blind)

Unstructured, but nearly acceptable –neurology example

- Endpoint a scale with range 0 to 80
- Lots of missing endpoint data
- Protocol says: use multiple imputation
- MI produces
  - Observations from –32 to 243
  - Silly values (43, 48, 32, 54, 3)
- Choose method reflecting intent of the framers

Unstructured, but nearly acceptable –malaria example

- Prior data: 30% of unpretreated kids get malaria
  - Malaria has many definitions
  - Fever, parasitemia, anemia
- Factorial –pretreat (Y/N), vaccine/placebo
- Interest in the vaccine/placebo comparison
- 3 months in trial, >90% unpretreated get malaria

Malaria, continued

	Pretreated		
	Yes	No	Total
Vaccine	?	?	?
Placebo	?	?	?
	30%	90%	

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- Know who is responsible for change (and keep good records!)

Benefits of allowing change

- Can save the trial
- Can save the team from its own errors
- Can lead to better more useful knowledge

But beware of risks!

- Generally-
  - A changed trial is less efficient than an unchanged one
  - The later the change, the less credible the results