Introduction to Crossover Trials

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Goa, India, September 2009

What Are Crossover Trials?

- Study is divided into periods and each subject receives a different treatment in each period
- Sequence of treatments is randomized
  - May be more than 2 treatments and periods
  - Subjects may each receive only subset of treatments
- Subjects “serve as own controls”

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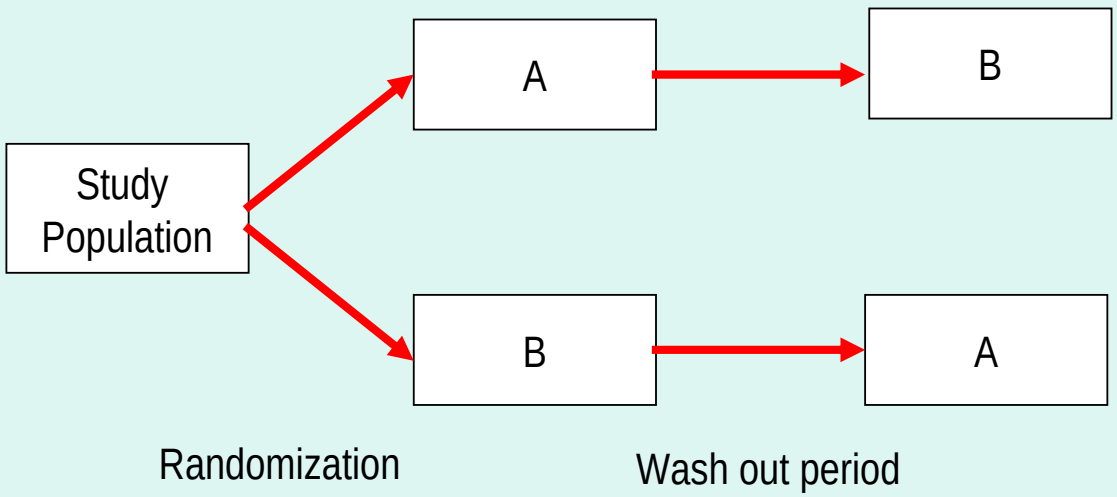
Simplest Crossover Design

- 2 treatments (A and B), 2 periods
- random assignment of subjects to AB or BA



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Advantages of Crossover Designs

- Each subject "serving as own control" implies less concern for baseline imbalance
- Can be much more efficient, if practical
  - Suppose treatment effect is difference in means
  - Variance for a parallel group trial, assuming equal variances, is $(2 / N) \sigma^2$
  - Variance for a crossover trial is $(2 / N) \sigma^2 (1 - \rho)$
    - ρ is correlation between responses from same subject
  - Ratio of 2 variances (design effect) is $(1 - \rho)$
  - Example: if $\rho = 0.75$, crossover design requires ¼ number of observations to attain equal precision

Potential Problems and Limitations

- Carryover!!
  - Treatments received in earlier periods may affect responses in later periods
  - Goal: avoid it through design
- Blinding – subjects able to compare drugs
- Assessing adverse events – which drug may have caused an event observed in period 2?
- Loss of subjects can cause problems, as usual
- Behavioral/educational interventions – how would you wash those out?

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Avoiding carryover “best done by selective and careful use of the design on the basis of adequate knowledge of both disease area and new medication.”

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Statistical Principles for Clinical Trials

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Practicalities

- Condition should be chronic and stable (period 1 treatment should not “cure” disease)
- The washout periods should be sufficiently long for complete reversibility of drug effects
- Treatment effects should be quickly observable
- Cross-over designs often used in phase I and II bioequivalence studies
  - pharmacokinetic studies in healthy volunteers

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Example

- Simplified slightly from Stokes, Davis, and Koch (2000) *Categorical Data Analysis Using SAS*
- 2-period crossover with 3 headache treatments (2 active drugs, A and B, and placebo, P)
  - Primary goal is to compare A and B
- Each subject randomized to one of 6 sequences:
  AB, BA, AP, PA, BP, PB
- Note that design is "incomplete" – each subject is "missing" one treatment

Observed Data

Sequence	Response Profiles				Total
	FF	FU	UF	UU	
A : B	12	12	6	20	50
B : A	19	3	25	3	50
A : P	25	6	6	13	50
P : A	5	3	22	20	50
B : P	8	5	6	31	50
P : B	13	5	21	11	50

F = favorable response; U = unfavorable response

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Analysis Method?

- Response in each period is binary: F or U
- Each person provides 2 responses
  - Do we expect responses to be independent?
- What are our analysis options?
  - Remember, primary concern is comparing A and B

How About GEE?

- Consider this model:

$$\text{logit}(\theta) = \beta_0 + \beta_1 * \text{DRUGA} + \beta_2 * \text{DRUGB} + \beta_3 * \text{PERIOD1} + \beta_4 * \text{CARRYA} + \beta_5 * \text{CARRYB}$$

where $\theta = \Pr\{ F \mid \text{drug, period, carry-over}\}$

DRUGA = 1 for A, 0 otherwise

DRUGB = 1 for B, 0 otherwise

PERIOD1 = 1 for period 1, 0 otherwise

CARRYA = 1 if period 2 AND drug in period 1 was A

CARRYB = 1 if period 2 AND drug in period 1 was B

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Carryover Effects

- We hope that there are none!
  - Makes interpretation very difficult
- But, it's a good idea to at least explore them
  - Test of carryover effects typically has low power
  - Remember, not finding them does not mean they are not there
- So, it's important to make them implausible by design using an appropriate washout period

Data in “Long” Form!

id	seq	response	drugA	drugB	period1	carryA	carryB
1	AB	F	1	0	1	0	0
1	AB	F	0	1	0	1	0
2	BA	F	0	1	1	0	0
2	BA	U	1	0	0	0	1
3	PA	U	0	0	1	0	0
3	PA	F	1	0	0	0	0

Let's Fit the Model!

- link = logit (for logistic regression)
- distribution or family = binomial
- corrtype or corr = exchangeable

Model Parameter Estimates

Parameter	Estimate		Standard Error	95% Confidence Limits		p-value
Intercept	$\beta_0 =$	-0.28	0.30	-0.87	0.30	0.343
drugA	$\beta_1 =$	1.18	0.21	0.77	1.59	<.001
drugB	$\beta_2 =$	0.33	0.22	-0.09	0.76	0.124
period1	$\beta_3 =$	-0.71	0.25	-1.21	-0.21	0.005
carryA	$\beta_4 =$	0.07	0.33	-0.57	0.72	0.823
carryB	$\beta_5 =$	0.04	0.33	-0.61	0.69	0.908

Reduced Model

- With individual p-values of 0.823 and 0.908, no evidence of carryover effects (good!)
  - Would be better to test parameters simultaneously using a 2 df test (p-value for this test is 0.975)

- So, we can fit reduced model

$$\text{logit}(\theta) = \beta_0 + \beta_1 * \text{DRUGA} + \beta_2 * \text{DRUGB} + \beta_3 * \text{PERIOD1}$$

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Model Parameter Estimates

Parameter	Estimate		Standard Error	95% Confidence Limits		p-value
Intercept	$\beta_0 =$	-0.23	0.15	-0.53	0.06	0.124
drugA	$\beta_1 =$	1.16	0.19	0.79	1.53	<.001
drugB	$\beta_2 =$	0.32	0.19	-0.05	0.69	0.088
period1	$\beta_3 =$	-0.74	0.15	-1.03	-0.45	<.001

- Pretty clear evidence that Drug A is better than placebo
- Drug B, not so much
- But primary concern is A vs. B…

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Answering the Primary Question

- How do drugs A and B compare?
- H_0: $\beta_1 - \beta_2 = 0$
- Estimated OR = exp{ 1.16 – 0.32 } = exp {0.84}

  = 2.31
- The odds of favorable response doubled with A
- 95% CI = (1.58, 3.37)
- p-value < 0.001

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"Only if there is substantial evidence that the therapy has no carryover effects, and the scientific community is convinced by that evidence, should a cross-over design be considered."

Friedman, Furberg, and DeMets

Fundamentals of Clinical Trials, 3rd ed. 1998

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