CLINICAL TRIAL DESIGNS FOR RARE DISEASES: CROSSOVER AND N-OF-1 TRIALS

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CROSS-OVER TRIALS

- Basic concept
  - Every subject is exposed to both treatments in different time intervals
  - Subjects are randomized to order in which they receive treatment or control
  - Don't have to worry about imbalance on prognostic factors; primary comparison is within subject
  - Attractive to study candidates, since assured of getting active treatment at some point

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  - Attractive to study candidates, since assured of getting active treatment at some point
  - **Since each subject serves as own control, need fewer subjects**

ADDITIONAL ISSUES

- Has to be a treatment taken regularly over time
  - Wouldn't apply to acute treatments, like antibiotics for infections, or treatment of asthmatic attack
- Need to randomize order of treatment
  - Treatment given first may tend to show better (or worse) outcome
- Subjects may be treated for more than 2 periods

EXAMPLE

- Two treatments to be compared
- Treatment interval of 2 weeks
- Required washout period of 1 week

Subject	Interval 1	W	Interval 2	W	Interval 3	W	Interval 4
001	A	a	B	a	B	a	A
002	B	s h	A	s h	B	s h	A
003	B	o u	A	o u	A	o u	B
004	A	t	B	t	A	t	B

POTENTIAL PROBLEM

- Possibility of carryover effects from one treatment phase to the next
- Dealt with by including a "washout" period during which no treatment is given
- Washout period must be long enough to ensure that prior treatment is not contributing to effect in next phase
- Hard to be sure how long washout period needs to be

EVALUATING CARRYOVER EFFECTS

- Statistical models can be developed to permit estimation of carryover effects, and testing for their presence
- If trial is powered to detect main effect, on assumption of zero carryover effect, the power to detect carryover effect will be low
- Dilemma: if we size trial to have good power to test for carryover effects, we lose the efficiency of the cross-over design

USE OF CROSS-OVER DESIGNS

- Bioequivalence trials
  - Trials in healthy volunteers to assess comparability of pharmacokinetic parameters of generic to marketed drug
- Medical areas requiring chronic administration of treatment
  - Epilepsy
  - Diabetes
  - Pain relief
  - Asthma

N-OF-1 DESIGNS

- Developed as a rigorous way to assess optimal treatment for an individual patient
- Works like a cross-over trial
  - Patient alternates between active treatment and placebo, or between alternative active treatment regimens
  - More than 2 periods usually necessary
  - To be informative, must see rapid improvement with one regimen, rapid decline when that regimen is withdrawn

EXAMPLE

- N-of-1 trial carried out to determine if oral theophylline was effective as part of asthma regimen
- Double-blind trial of 10-day treatment periods on either treatment or placebo
- Outcomes assessed by patient self-report on 7-point scale (1 worst)
  - Shortness of breath
  - Need for albuterol for acute symptoms
  - Sleep disturbance

EXAMPLE: RESULTS

SYMPTOM	DRUG	PLACEBO	DRUG	PLACEBO
Shortness of breath	3	6	3	6
Need for inhaler	3	5.5	3	5
Sleep disturbance	5	5.5	3	5

Guyatt et al, NEJM, 1986

EXTENSION TO POPULATION STUDIES

- N-of-1 trials could be used in early stage of drug development to facilitate design and conduct of definitive trials
  - Estimate proportion of responders
  - Study dosage
- Statistical model for combining n-of-1 trials to estimate effects in population has been developed (Zucker et al, J Clin Epid, 1997)

LIMITS OF N-OF-1 STUDIES

- As with cross-over studies, issue is interference over treatment periods
- Washout period required; need to know required length to avoid carryover effect
- Most applicable to chronic conditions where alleviation of symptoms is treatment goal
- Could also be used to assess biomarker changes if carefully monitored to keep subjects out of danger zone