

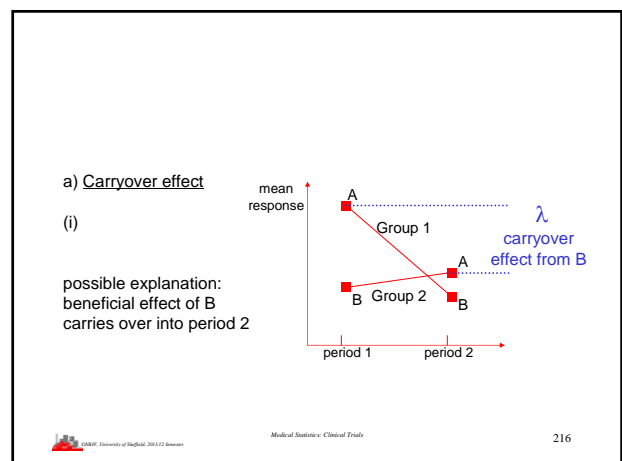
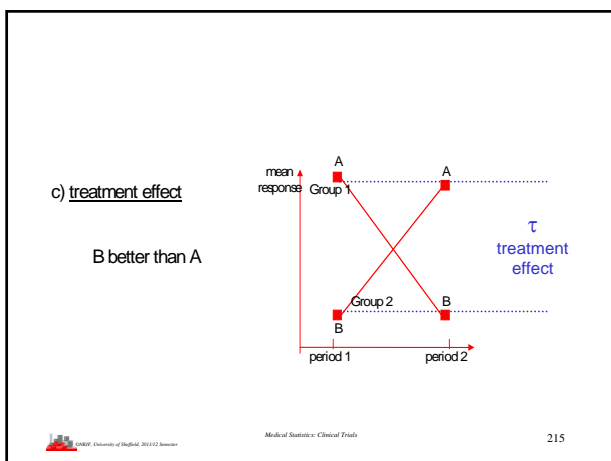
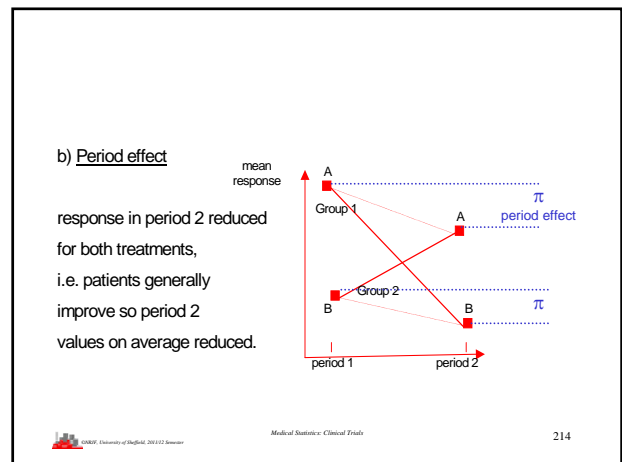
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- Two Treatment Two Period Trial
 - ◆ Patients receive both treatments
 - Group 1 in order A then B
 - Group 2 in order B then A
 - ◆ Treatment comparisons *within patients*
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- Possible effects:
 - ◆ treatment effects τ
 - ◆ period effect π
 - ◆ carryover effect λ
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Carryover effect
(ii)

Direction of treatment effect different for different periods caused by carryover.

(ii) is more serious, (i) is unlikely to be detected because of low power.

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Model:

- ◆ $Y_{ijk} = \mu + \alpha_k + \tau + \pi + \lambda + \varepsilon_{ijk}$
- ◆ $E(Y_{11k}) = \mu + \tau_A + \pi_1$
- ◆ $E(Y_{12k}) = \mu + \tau_B + \pi_2 + \lambda_A$
- ◆ Where α_k — random patient effect
 - $\sim N(0, \phi^2)$ (between patients)
- ◆ ε_{ijk} — random errors
 - $\sim N(0, \sigma^2)$ (independently)

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Can then test for

- ◆ carryover λ ,
- ◆ period π
- ◆ treatment τ

with t-tests on various sums and differences of the Y_{ijk} 's

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Carryover effect

- ◆ T_{ik} = the average of 2 values for patient k.
- ◆ If no carryover then these should be same whatever the order of treatments, i.e. same for groups 1 and 2
- ◆ Use two-sample t-test to check this on T_{ik}

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Use

$$\frac{\bar{T}_1 - \bar{T}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}} \sim t_r$$

If significant then evidence of carryover

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Treatment & period effects

D_{ik} = within subject differences

- ◆ Then
 - $D_{1k} \sim N((\tau_A - \tau_B) + (\pi_1 - \pi_2), 2\sigma^2)$ group 1
 - $D_{2k} \sim N((\tau_B - \tau_A) + (\pi_1 - \pi_2), 2\sigma^2)$ group 2

Difference removes $(\pi_1 - \pi_2)$
Sum removes $(\tau_A - \tau_B)$

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■ Treatment test:

$$\frac{\bar{D}_1 - \bar{D}_2}{\sqrt{\frac{SD_1^2}{n_1} + \frac{SD_2^2}{n_2}}} \sim t_r$$

- ◆ NB SD_1^2 variance of **differences** D_{1k}
- ◆ If significant then evidence of treatment differences

■ Period test

- ◆ D_{1k} and $-D_{2k}$ have the same means if no period effect so use two sample t-test of D_{1k} against $-D_{2k}$

■ i.e. use

$$\frac{\bar{D}_1 - (-\bar{D}_2)}{\sqrt{\frac{SD_1^2}{n_1} + \frac{SD_2^2}{n_2}}} \sim t_r$$

- If significant then evidence of difference between periods, i.e. change over time.

- Test for carryover has low power
- Supplement by medical knowledge
 - ◆ i.e. need expert opinion that either
 - ◆ treatments cannot interact
 - or
 - ◆ washout period sufficient,
- cannot rely purely on statistical evidence.

■ Binary Responses

- ◆ key idea is to consider *within subject* comparisons
- ◆ consider whether the difference between the responses to the two treatments for the same subject indicates treatment A is 'better' or 'worse' than treatment B
 - If the responses are identical then subject provides no information on treatment differences

■ Example

- ◆ Two treatments F and S
 - Result recorded is which is preferable
- ◆ To test for differences between **treatments**
 - Consider whether preference for **first period** treatment depends on order given (i.e. between two groups)
- ◆ To test for differences between **periods**
 - Consider whether preference for **treatment F** depends on order given (i.e. between two groups)



sequence	preference		total
	first period	second period	
for → sal	9	0	9
sal → for	1	6	7
total	10	6	16

- Pearson chi-squared test statistic is $(9 \times 6 - 1 \times 0)^2 \times 16 / [10 \times 6 \times 7 \times 9] = 12.34$
significant $p < 0.001$
 - ♦ so data provide strong evidence of superiority of the treatment by formoterol
- (Mainland-Gart Test)

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sequence	preference		total
	formoterol	salbutamol	
for → sal	9	0	9
sal → for	6	1	7
total	15	1	16

- Now the test statistic is $(9 \times 1 - 6 \times 0)^2 \times 16 / [15 \times 1 \times 7 \times 9] = 1.37$
 - ♦ no evidence of a period effect

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- **Summary and Conclusions**
 - ♦ **carryover**:– 2-sample test on average
 - over both periods
 - ♦ **period**:– 2-sample test on differences
 - treatment A – treatment B
 - ♦ **treatment**:–2-sample test on differences
 - period I – period II

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- **Mnemonic**:–
 - ♦ Test for **period** by 2-sample test on **treatment differences**
 - ♦ Test for **treatment** by 2-sample test on **period differences**

(X-over trial)

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- Carryover ≡ treatment × period interaction
 - ♦ If present then use only period 1 results
 - treatment comparisons then **between** subjects
 - preliminary test for carryover **not recommended** by some authorities
 - preferable to rely upon medical considerations to eliminate the possibility of a carryover

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- A full crossover analysis gives a **within** subject comparison
 - ♦ if normality then two sample t-tests
 - ♦ If not replace with non-parametric tests
 - e.g. Wilcoxon-Mann-Whitney
 - ♦ Mainland-Gart test for binary responses
 - considers only those subjects exhibiting different responses to the treatments

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