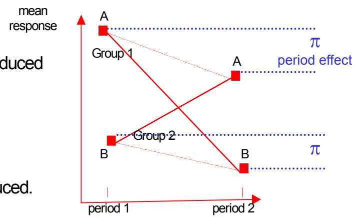
Contents

- 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***

- Possible effects:
  - treatment effects τ
  - period effect π
  - carryover effect λ

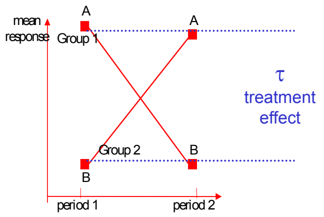
b) Period effect

response in period 2 reduced for both treatments, i.e. patients generally improve so period 2 values on average reduced.



c) treatment effect

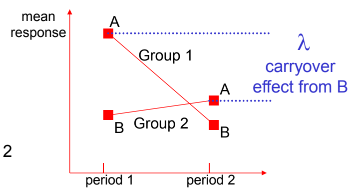
B better than A



a) Carryover effect

(i)

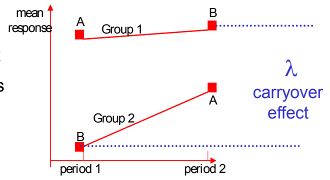
possible explanation:
beneficial effect of B
carries over into period 2



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.

- 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)

- Can then test for
  - carryover λ,
  - period π
  - treatment τ

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

- **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}

- 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

- **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 $(\tau_A - \tau_B)$

- Treatment test:

$$\frac{\bar{D}_1 - \bar{D}_2}{\sqrt{\frac{s_{D1}^2}{n_1} + \frac{s_{D2}^2}{n_2}}} \sim t_r$$

  - NB s_{D1}^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 ttest of D_{1k} against $-D_{2k}$

- i.e. use

$$\frac{\bar{D}_1 - (-\bar{D}_2)}{\sqrt{\frac{s_{D1}^2}{n_1} + \frac{s_{D2}^2}{n_2}}} \sim t_r$$

- 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 chisquared 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)

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

- **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

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

(X-over trial)

- 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

- 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