CHL 5225 H Crossover Trials

The Two-sequence, Two-Treatment, Two-period Crossover Trial

Definition

A trial in which patients are randomly allocated to one of two sequences of treatments (either 1 then 2, or 2 then 1) so that within-patient differences can be used to compare treatments (*i.e.* patients can be used as their own control)

Patients must stop the first treatment and either start the second or enter a wash-out period at a predetermined point in time which is the same for all patients

CHL 5225 H Crossover Trials

		Period	
		1	2
Sequence (order)	1→2	Patient receives Treatment 1	Patient receives Treatment 2
	2→1	Patient receives Treatment 2	Patient receives Treatment 1

CHL 5225 H Crossover Trials

Blocking

Blocking may be employed to ensure roughly the same number of patients in each sequence

Stratification

Blocking within strata to balance for prognostic factors is usually not necessary since patients are their own control

CHL 5225 H Crossover Trials

Appropriate Diseases and Conditions

Chronic, relatively stable

Manifest as patient symptoms or disability

Cyclical conditions such as nausea/vomiting with chemotherapy

Appropriate Treatments

Transient, non-curative

Provide symptom relief

Short half-lives

CHL 5225 H Crossover Trials

Appropriate Measurements

Subjective – symptom scores, ratings of pain, *etc*.

Objective – strength

Preference – which treatment period did the patient prefer

CHL 5225 H Crossover Trials

Blinding

Whenever possible patients, clinicians and observers (research staff) should be Blinded (masked) to treatment sequence and, if possible, unaware of the time at which the crossover from one treatment to the other occurs

Other Design Features

Possible “wash-out” period between treatment periods

Possible baseline measurements prior to both treatment periods

CHL 5225 H Crossover Trials

Advantages

Treatments are compared within patients, thereby the influence

of patient factors (age, sex, disease severity) are “subtracted out”;

that is, the between-patient variance is removed,

leading to:

- smaller variances
- increase power
- smaller required sample sizes

CHL 5225 H Crossover Trials

Advantages

$$N = 4\left\{\frac{(z_{1-\alpha/2} + z_{1-\beta})\sigma}{\delta}\right\}^2$$

N = number of patients required for a parallel groups trial,

$$n = 2\left\{\frac{(z_{1-\alpha/2} + z_{1-\beta})\sigma}{\delta}\right\}^2 (1-\rho)$$

where n = number of patients required for a crossover trial

and

ρ= is the correlation between measurements made on the same patient

CHL 5225 H Crossover Trials

Advantages

$$\frac{n}{N} = \frac{1-\rho}{2}$$

Typically ρ is between 0.3 and 0.6

For $\rho = 0.5$ $\quad \frac{n}{N} = \frac{1}{4}$

CHL 5225 H Crossover Trials

Advantages

Permits the use of preference data, which is particularly useful if a validated instrument for measuring outcome or disease status is not available

CHL 5225 H Crossover Trials

Disadvantages

Short time frame does not permit the assessment of long term benefits and harms

Crossover trial can be used because patients are more likely to consent

Period effect – disease not a stable as expected

CHL 5225 H Crossover Trials

Disadvantages

Bad press:

1977 report of the Biometric and Epidemiology Methodolgical Advisory Committee of the US FDA states that “the two-period crossover design is not the design of choice in clinical trials where unequivocal evidence of Trt effects is required.”

CHL 5225 H Crossover Trials

Disadvantages

Treatment by period interaction

- sequence (order) effect
- residual carryover
- partially confounds treatment effect

i.e. produces biased estimates of Treatment effect

More suitable for an early phase III trial

CHL 5225 H Crossover Trials

Parametric model for continuous outcome

i = 1: treat. 1 → treat. 2
i = 2: treat. 2 → treat. 1

Let Y_{ijk} be the observed outcome on the j^{th} patient ($j = 1, 2, \ldots n_i$)

randomized to the i^{th} sequence ($i = 1, 2$) during the k^{th} period ($k = 1, 2$)

$$Y_{ijk} = \mu + \pi_k + \phi_{v(i,k)} + (k-1)\lambda_i + \xi_{ij} + \varepsilon_{ijk}$$

where

$\mu = \text{overall mean}$

$\pi_k = \text{effect of } k^{th} \text{ period}, \pi_1 + \pi_2 = 0$

$\phi_{v(i,k)} = \text{effect of treatment } v(i,k) = i * k (\text{mod} 3), \quad \phi_1 + \phi_2 = 0$

$\lambda_i = \text{the carryover effect of treatment } i \text{ from period 1 to period 2}$

$\xi_{ij} = \text{effect of } j^{th} \text{ patient in the } i^{th} \text{ order}$

$\varepsilon_{ijk} = \text{the within} - \text{patient deviation for period } k$

CHL 5225 H Crossover Trials

$\xi_{ij} \sim N(0, \sigma^2_\xi)$ and $\varepsilon_{ijk} \sim N(0, \sigma^2_\varepsilon)$, mutally independent

$$\text{Cov}\left(Y_{ijk}, Y_{ijk'}\right) = \begin{cases} \sigma^2_\xi + \sigma^2_\varepsilon : k = k' \\ \sigma^2_\xi : k \neq k' \end{cases}$$

$$\text{Corr}\left(Y_{ij1}, Y_{ij2}\right) = \frac{\sigma^2_\xi}{\sigma^2_\xi + \sigma^2_\varepsilon} = \rho$$

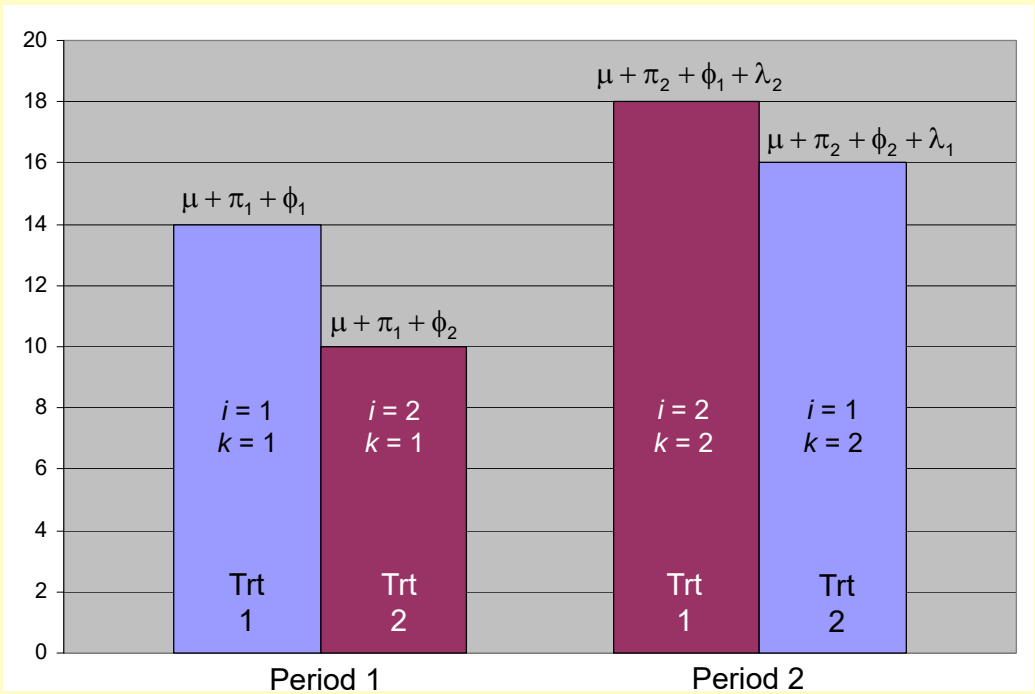
Finally, let

$\pi = \pi_2 - \pi_1$ (period effect)

$\phi = \phi_2 - \phi_1$ (treatment effect)

$\lambda = \lambda_2 - \lambda_1$ (residual carryover) (a.k.a. treatment by period interaction a.k.a. sequence effect)

Means by Period and Trt



CHL 5225 H Crossover Trials

$$Y_{i.k} = \frac{1}{n_i}\sum_{j=1}^{n_i} Y_{ijk}$$

Sequence (order)	Period k = 1	Period k = 2
1→2 (i = 1)	$E(Y_{1.1}) = \mu + \pi_1 + \phi_1$	$E(Y_{1.2}) = \mu + \pi_2 + \phi_2 + \lambda_1$
2→1 (i = 2)	$E(Y_{2.1}) = \mu + \pi_1 + \phi_2$	$E(Y_{2.2}) = \mu + \pi_2 + \phi_1 + \lambda_2$

Treatment effect in Period 1: $E(Y_{2.1}) - E(Y_{1.1}) = \phi_2 - \phi_1 = \phi$

Treatment effect in Period 2: $E(Y_{1.2}) - E(Y_{2.2}) = \phi_2 - \phi_1 + \lambda_1 - \lambda_2 = \phi - \lambda$

Therefore, Treatment X Period interaction exists $\Leftrightarrow \lambda \neq 0$

Effect of Sequence 1: $\{E(Y_{1.1}) + E(Y_{1.2})\}/2 = (2\mu + \pi_1 + \pi_2 + \phi_1 + \phi_2 + \lambda_1)/2$

Effect of Sequence 2: $\{E(Y_{2.1}) + E(Y_{2.2})\}/2 = (2\mu + \pi_1 + \pi_2 + \phi_1 + \phi_2 + \lambda_2)/2$

Sequence effect: $(\lambda_2 - \lambda_1)/2 = \lambda/2$

Therefore, Sequence effect exists $\Leftrightarrow \lambda \neq 0$

CHL 5225 H Crossover Trials

Sequence (order)	Period k = 1	Period k = 2
1→2 (i = 1)	$E(Y_{1.1}) = \mu + \pi_1 + \phi_1$	$E(Y_{1.2}) = \mu + \pi_2 + \phi_2 + \lambda_1$
2→1 (i = 2)	$E(Y_{2.1}) = \mu + \pi_1 + \phi_2$	$E(Y_{2.2}) = \mu + \pi_2 + \phi_1 + \lambda_2$

Estimator of Treatment effect in Sequence 1: $Y_{1.2} - Y_{1.1}$

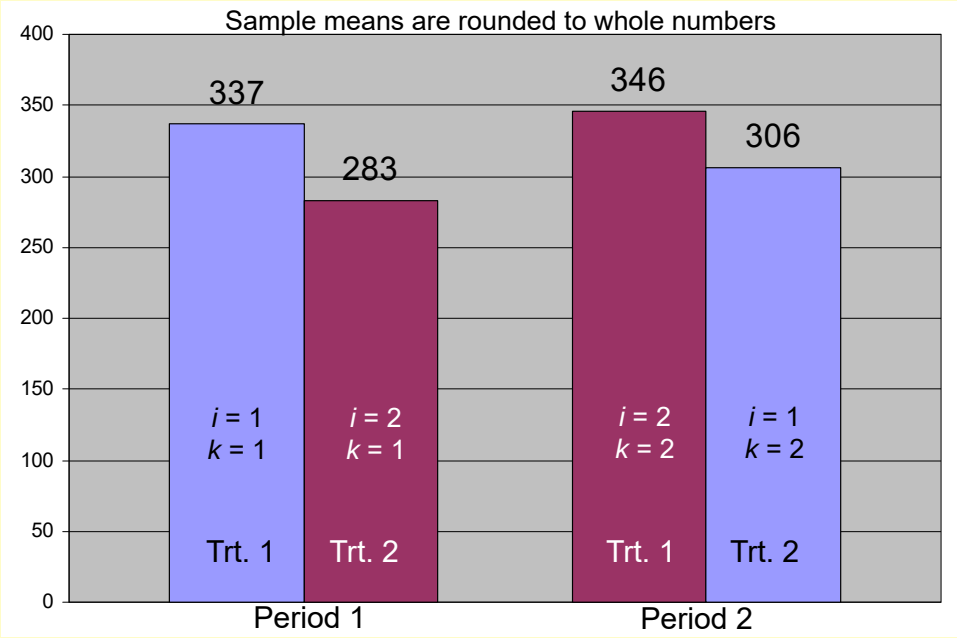
Estimator of Treatment effect in Sequence 2: $Y_{2.1} - Y_{2.2}$

Expected value of overall estimator of Treatment effect:

$$= E\left[(Y_{1.2} - Y_{1.1} + Y_{2.1} - Y_{2.2})/2\right]$$
$$= \left[E(Y_{1.2}) - E(Y_{1.1}) + E(Y_{2.1}) - E(Y_{2.2})\right]/2$$
$$= \left[\phi_2 + \lambda_1 - \phi_1 + \phi_2 - (\phi_1 + \lambda_2)\right]/2$$
$$= \phi - \lambda/2$$

Overall estimator of Treatment effect is biased $\Leftrightarrow \lambda \neq 0$

sequence	patient	period	treatment	outcome	sex
1	1	1	1	310	m
1	1	2	2	270	m
1	2	1	1	310	m
1	2	2	2	260	m
1	3	1	1	370	f
1	3	2	2	300	f
1	4	1	1	410	m
1	4	2	2	390	m
1	5	1	1	250	m
1	5	2	2	210	m
1	6	1	1	380	f
1	6	2	2	350	f
1	7	1	1	330	m
1	7	2	2	365	m
2	8	1	2	370	f
2	8	2	1	385	f
2	9	1	2	310	f
2	0	2	1	400	f
2	10	1	2	380	m
2	10	2	1	410	m
2	11	1	2	290	m
2	11	2	1	320	m
2	12	1	2	260	m
2	12	2	1	340	m
2	13	1	2	90	m
2	13	2	1	220	m



$$\hat{\phi} = \{(306 - 337) + (283 - 346)\}/2 = -47$$

$$\hat{\pi} = \{(346 - 337) + (306 - 283)\}/2 = 16$$

$$\hat{\lambda}/2 = \{(283 - 337) - (306 - 346)\}/2 = -7$$

CHL 5225 H Crossover Trials

SAS code for the analysis of the 2 X 2 X 2 crossover trial

```
proc MIXED data=sasf.xOverExampleData;
   class patient;
   model outcome = sequence period treatment / solution;
   repeated / subject=patient type=cs r rcorr;
   title 'All Patients';
run;
```

Because of the coding (1, 2) we don't need to declare as class variable. Will give means "2" minus "1"

CHL 5225 H Crossover Trials

Alternative SAS code for the analysis of the 2 X 2 X 2 crossover trial

```
proc MIXED data=sasf.xOverExampleData;
   class patient sequence period treatment;
   model outcome = sequence period treatment;
   repeated / subject=patient type=cs r rcorr;
   estimate 'PHI' treatment -1 2;
   estimate 'PI' period -1 2;
   estimate 'LAMBDA/2' sequence -1 2;
   title 'All Patients';
run;
```

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	375.06	65.8524	11	5.70	0.0001
sequence ($\hat{\lambda}/2$)	-7.2024	40.2026	11	-0.18	0.8611
period ($\hat{\pi}$)	15.8929	10.7766	11	1.47	0.1683
treatment ($\hat{\phi}$)	-46.6071	10.7766	11	-4.32	0.0012

Estimated R Correlation Matrix for patient 1

Row	Col1	Col2
1	1.0000	0.8659 ← $\hat{\rho}$
2	0.8659	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
CS	patient	4846.54 ← $\hat{\sigma}^2_{\xi}$
Residual		750.41 ← $\hat{\sigma}^2_{\varepsilon}$

$$\hat{\rho} = \frac{\hat{\sigma}^2_{\xi}}{\hat{\sigma}^2_{\xi} + \hat{\sigma}^2_{\varepsilon}} = 4846.54/(4846.54 + 750.42) = 0.8659$$

CHL 5225 H Crossover Trials

Covariates—examining subgroups

```
data temp; set sasf.xOverExampleData;
    m1f0 = 1; if sex eq 'f' then m1f0 = 0;
    m0f1 = 1; if sex eq 'm' then m0f1 = 0;
run;


proc MIXED data=temp;
    class patient;
    model outcome = sequence period treatment m1f0 m1f0*treatment
            / solution;
    repeated / subject=patient type=cs r rcorr;
    title 'Effect in Female Patients';
run;


proc MIXED data=temp;
    class patient;
    model outcome = sequence period treatment m0f1 m0f1*treatment
        / solution;
    repeated / subject=patient type=cs r rcorr;
    title 'Effect in Male Patients';
run;
```

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	426.34	76.0138	10	5.61	0.0002
sequence	-9.9569	38.6755	10	-0.26	0.8021
period	15.7328	11.2746	10	1.40	0.1931
treatment	-51.2500	20.2386	10	-2.53	0.0298
m1f0	-67.9310	55.4962	10	-1.22	0.2490
treatment*m1f0	6.7241	24.3560	10	0.28	0.7881

Trt effect in females

Test for interaction→
i.e. Trt effect in females = Trt effect in males

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	358.41	65.5131	10	5.47	0.0003
sequence	-9.9569	38.6755	10	-0.26	0.8021
period	15.7328	11.2746	10	1.40	0.1931
treatment	-44.5259	13.5504	10	-3.29	0.0082
m0f1	67.9310	55.4962	10	1.22	0.2490
treatment*m0f1	-6.7241	24.3560	10	-0.28	0.7881

Trt effect in males

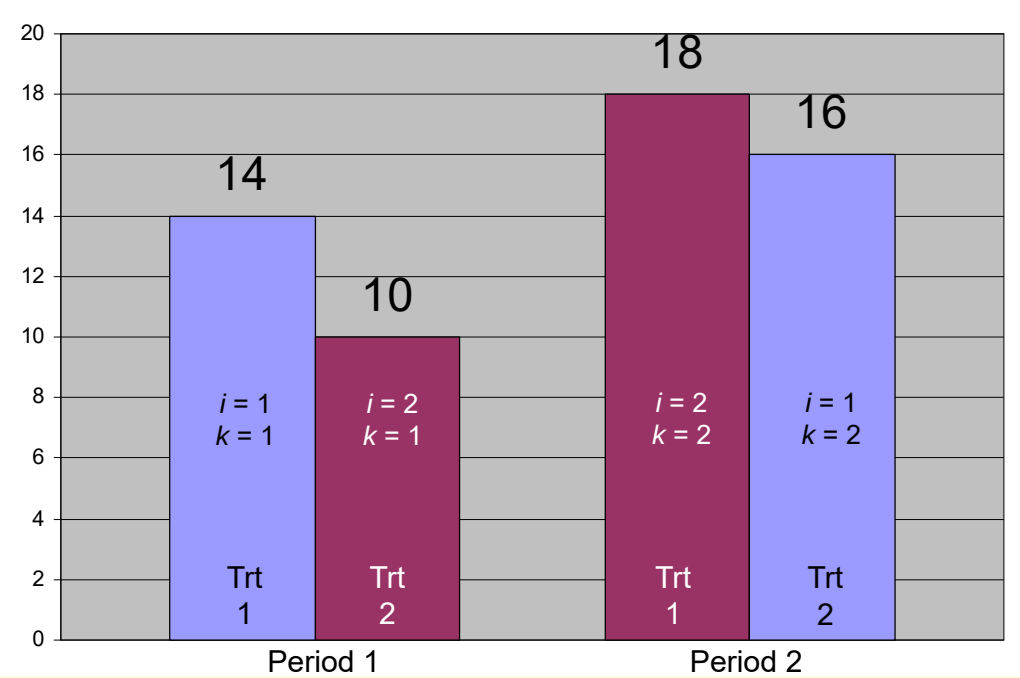
CHL 5225 H Crossover Trials

Test for treatment effect (*i.e.* H: $\phi = 0$) is valid $\Leftrightarrow \phi = 0 \Rightarrow \lambda = 0$

When might this be true?

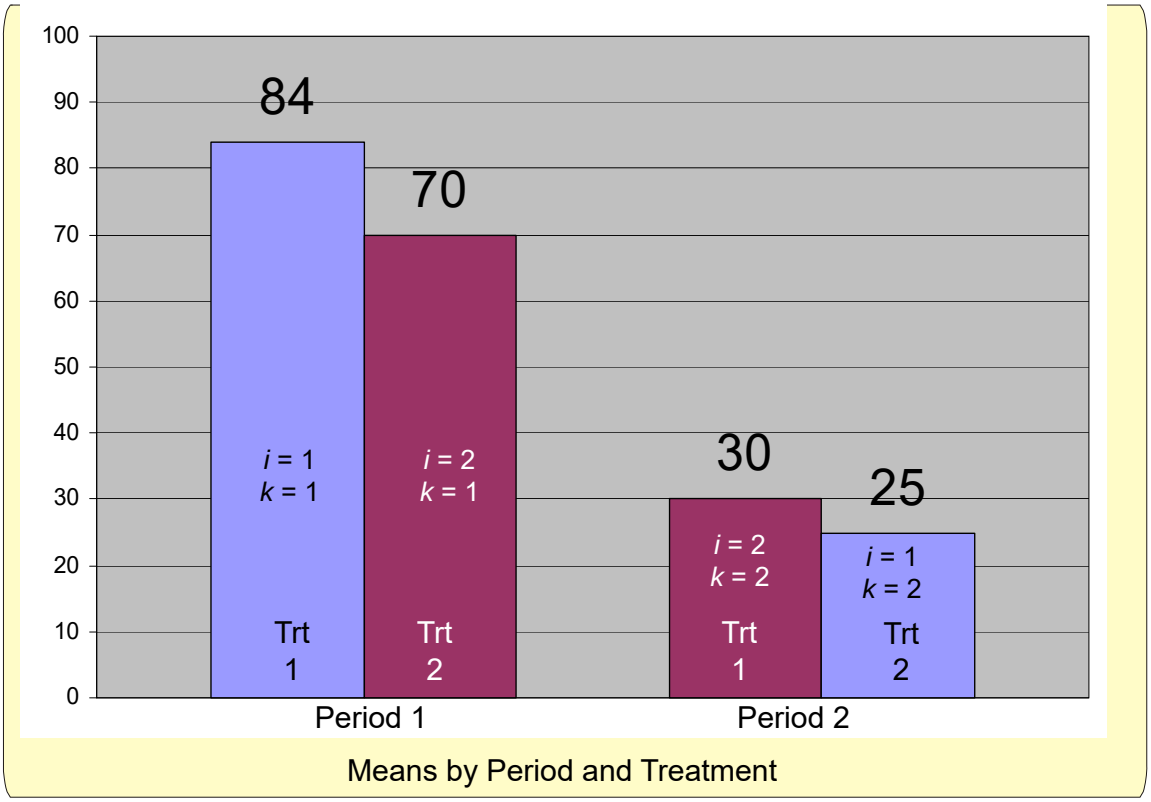
- Placebo-controlled trial
- Differential conditioning (nausea example)
- Floor effect (caused by strong period effect)
- "Unmasking" (leading to an over estimate of treatment effect in 2nd period)

Differential conditioning (nausea example)



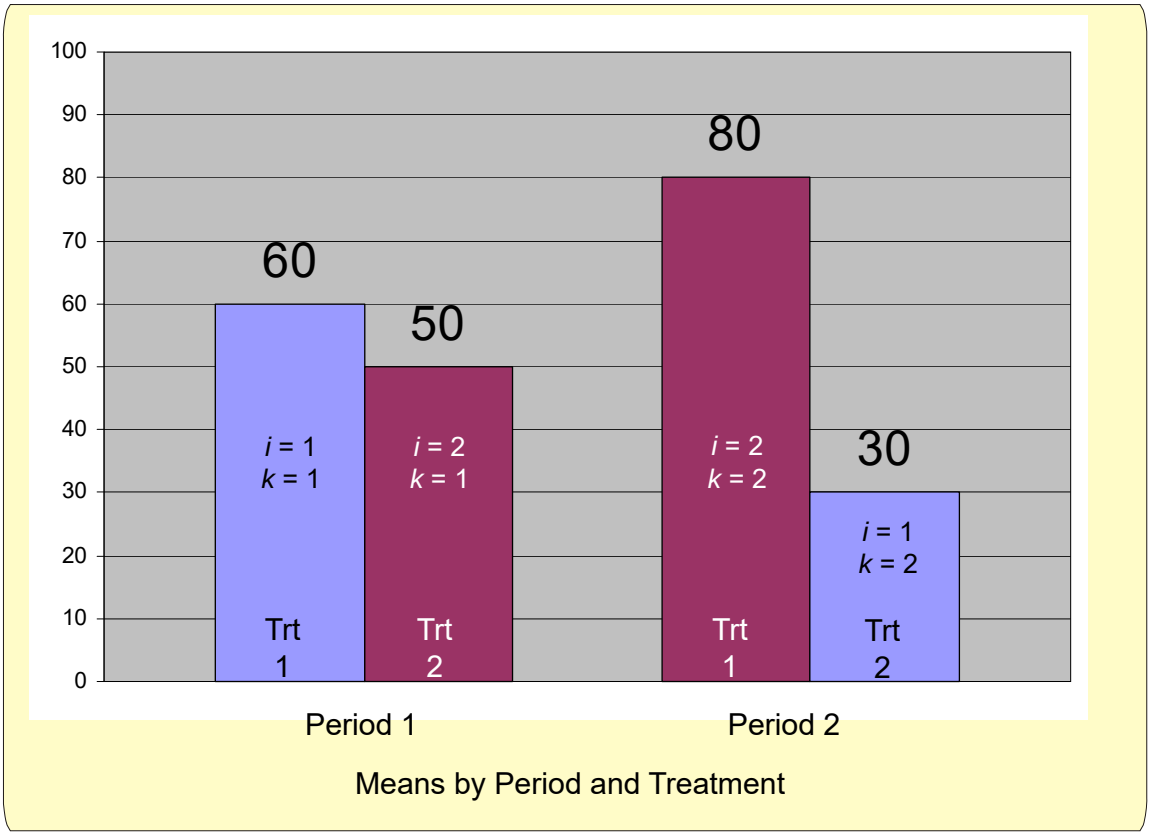
Means by Period and Treatment

Floor effect (caused by strong period effect)



Means by Period and Treatment

"Unmasking"



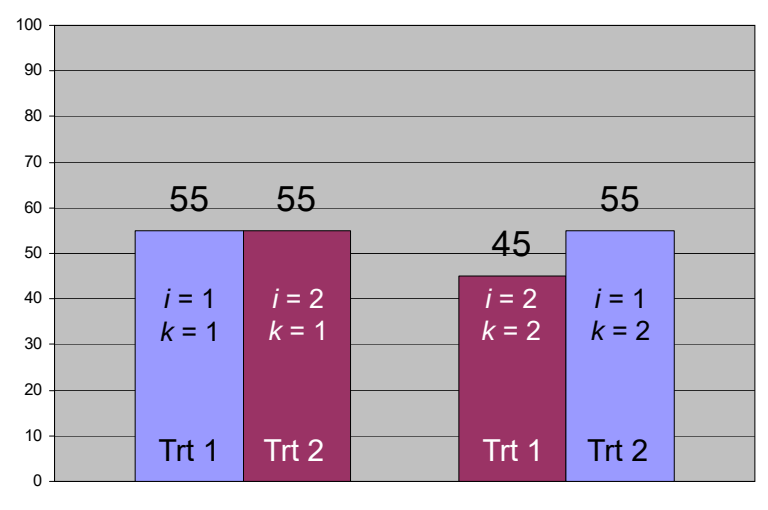
Means by Period and Treatment

CHL 5225 H Crossover Trials

Gotta watch out for $\phi = 0 \not\Rightarrow \lambda = 0$

$\hat{\phi} = (0 + 5)/2 = 2.5$ (favours treatment 1)

This implies physical carryover, and the analysis must be restricted to Period 1 data only (a two-sample t-test or comparable non-parametric test)



CHL 5225 H Crossover Trials

But even if $\phi = 0 \Rightarrow \lambda = 0$, and therefore test of null hypothesis is valid,

$E(\hat{\phi}) = \phi - \lambda/2$ and is therefore biased

Only way to avoid bias is to use first period data only, that is

$\hat{\phi}_{P.1} = Y_{2.1} - Y_{1.1}$

$$V(\hat{\phi}) = \{(n_1 + n_2)/(n_1 n_2)\}\frac{\sigma_\varepsilon^2}{2}$$

$$V(\hat{\phi}_{P.1}) = \{(n_1 + n_2)/(n_1 n_2)\}(\sigma_\xi^2 + \sigma_\varepsilon^2)$$

$$V(\hat{\phi})/V(\hat{\phi}_{P.1}) = (1 - \rho)/2$$

CHL 5225 H Crossover Trials

The test of hypothesis based on $\hat{\phi}$ has more power
(*i.e.* has a greater probability of rejecting the null hypothesis when it is false)
than the test based on $\hat{\phi}_{P.1}$

$\Leftrightarrow \lambda/\phi < 2 - \sqrt{2(1-\rho)}$

Willan and Pater *Biometrics* 1986; **42**:593-599

Willan *Biometrics* 1988; **44**:211-218

ρ	$2 - \sqrt{2(1-\rho)}$
0	0.586
0.3	0.816
0.5	1.00

CHL 5225 H Crossover Trials

When does $\lambda/\phi < 2 - \sqrt{2(1-\rho)}$ hold?????

Well

$\hat{\lambda}/\hat{\phi}_{P.1} < 2 - \sqrt{2(1-\hat{\rho})}$ holds $\Leftrightarrow$ |test statistic($\hat{\phi}$)| > |test statistic($\hat{\phi}_{P.1}$)|

where $\hat{\rho} = \dfrac{\hat{\sigma}^2_\xi}{\hat{\sigma}^2_\xi + \hat{\sigma}^2_\varepsilon}$ is the estimate of ρ

Willan (1988) suggests basing analysis on the test statistic with the largest absolute value
i.e. declare significance if either one is significant

Introduces multiplicity

Therefore must adjust level of significance to maintain type I error probability

CHL 5225 H Crossover Trials

$\hat{\rho}$	Nominal level for 0.05	Nominal level for 0.025
0	0.03037	0.01469
0.1	0.02974	0.01441
0.2	0.02917	0.01414
0.3	0.02864	0.01390
0.4	0.02814	0.01368
0.5	0.02766	0.01348
0.6	0.02721	0.01329
0.7	0.02679	0.01311
0.8	0.02637	0.01295
0.9	0.02594	0.01279
1	0.02532	0.01258

CHL 5225 H Crossover Trials

```
proc MIXED data=sasf.xOverExampleData;
    class patient;
    model outcome = sequence period treatment / solution;
    repeated / subject=patient type=cs r rcorr;
    title 'All Patients';
run;


proc glm data=sasf.xOverExampleData;
    where period eq 1;
    model outcome = treatment / solution;
    title 'Period 1 Data Only';
run;
```

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	375.06	65.8524	11	5.70	0.0001
sequence	-7.2024	40.2026	11	-0.18	0.8611
period	15.8929	10.7766	11	1.47	0.1683
treatment	-46.6071	10.7766	11	-4.32	0.0012

Estimated R Correlation

Row	Col1	Col2
1	1.0000	0.8659
2	0.8659	1.0000

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	390.9523810	69.92825490	5.59	0.0002
treatment	-53.8095238	45.28386839	-1.19	0.2597

CHL 5225 H Crossover Trials

Reject null hypothesis:

if the maximum of |-4.32| or |-1.19| exceeds cut-off point

or equivalently

if the smallest associated p-value is less than nominal value from the table

for two-sided test, smallest associated p-value is min. of (0.0012, 0.257)

for one-sided test, smallest associated p-value is min. of $\left(\frac{0.0012}{2}, \frac{0.2597}{2} \right)$

Use nominal level of 0.02594 to achieve a type I error probability of 0.05

CHL 5225 H Crossover Trials

Grizzle Procedure Grizzle JE. *Biometrics* 1965; **21**: 467-480.

Test $H_\lambda : \lambda = 0$ using a two-sided level of 0.1

If H_λ is rejected then use period 1 data only

If H_λ is not rejected then use data from both periods

Not an issue of statistical inference (sample size being the biggest determinant of significance)

The issue is the size of λ and whether it is likely to be non-zero if $\phi = 0$

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	375.06	65.8524	11	5.70	0.0001
sequence	-7.2024	40.2026	11	-0.18	0.8611
period	15.8929	10.7766	11	1.47	0.1683
treatment	-46.6071	10.7766	11	-4.32	0.0012

Since p-value > 0.1,
Use data from both periods

Estimated R Correlation

Row	Col1	Col2
1	1.0000	0.8659
2	0.8659	1.0000

Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	390.9523810	69.92825490	5.59	0.0002
treatment	-53.8095238	45.28386839	-1.19	0.2597

CHL 5225 H Crossover Trials

Missing Second Period Data

Analyze complete data (*i.e.* patients with period 1 & 2 data) as before

Yields: $\hat{\phi}_C$ and $V(\hat{\phi}_C)$ $(= SE^2)$

$df_C = m_C - 2$, where m_C = # patients with complete data

Analyze incomplete (*i.e.* patients with period 1 data only) data as 2-sample t-test

Yields: $\hat{\phi}_{INC}$ and $V(\hat{\phi}_{INC})$ $(= SE^2)$

$df_{INC} = m_{INC} - 2$, where m_{INC} = # patients with missing period 2 data

CHL 5225 H Crossover Trials

Missing Second Period Data

$$\hat{\phi} = V(\hat{\phi})\left(\frac{\hat{\phi}_C}{V(\hat{\phi}_C)} + \frac{\hat{\phi}_{INC}}{V(\hat{\phi}_{INC})}\right), \text{ where } V(\hat{\phi}) = \left(\frac{1}{V(\hat{\phi}_C)} + \frac{1}{V(\hat{\phi}_{INC})}\right)^{-1}$$

$$t_{df_C + df_{INC}} = t_{m_C + m_{INC} - 4} = t_{n_1 + n_2 - 4} = \hat{\phi} \Big/ \sqrt{V(\hat{\phi})}$$

Where n_i = # of patients randomized to sequence i

There fore $m_C + m_{INC} = n_1 + n_2$

CHL 5225 H Crossover Trials

Binary Outcome (1 = success; 0 = failure)

	(outcome period 1, outcome period 2)					
Sequence	(0,0)	(0,1)	(1,0)	(1,1)	Total	
1 (1,2)	12	41	18	9	80	59
2 (2,1)	10	23	38	11	82	61
Total	22	64	56	20	162	120

Analyze "red" table using methods appropriate for testing for association in a 2 x 2 table

Fisher Exact test

Chi-squared tests

Use Fisher exact or continuity-corrected Chi-square for small cell frequencies

Valid in the presence of period effect, but NOT in the presence of a physical residual carryover effect

CHL 5225 H Crossover Trials

sequence y

Frequency Row Pct	1	2	Total
1	41 69.49	18 30.51	59
2	23 37.70	38 62.30	61
Total	64	56	120

Statistics for Table of sequence by y

Statistic	DF	Value	Prob
Chi-Square	1	12.1754	0.0005
Likelihood Ratio Chi-Square	1	12.4011	0.0004

Fisher's Exact Test

Cell (1,1) Frequency (F)	41
Left-sided Pr <= F	0.9999
Right-sided Pr >= F	0.0004
Table Probability (P)	0.0003
Two-sided Pr <= P	0.0005

CHL 5225 H Crossover Trials

Alternatively, could use PROC GENMOD in SAS

Patient	Sequence	Period	Treatment	Outcome
1	1	1	1	0
1	1	2	2	0
2	2	1	2	1
2	2	2	1	0
ect.				

```
proc genmod data=binaryXover;
  class patient;
  model outcome = sequence period treatment
      / dist=bin link=logit;
  repeated subject=patient / type=exch;
run;
```

CHL 5225 H Crossover Trials

```
Exchangeable Working
     Correlation

Correlation    -0.456105135


GEE Fit Criteria

QIC           437.9565
QICu          437.9565


Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

                  Standard   95% Confidence
Parameter Estimate    Error       Limits            Z Pr > |Z|

Intercept   1.9668   0.6594   0.6744   3.2592    2.98   0.0029
sequence   -0.1071   0.1701  -0.4405   0.2264   -0.63   0.5292
period     -0.2226   0.2760  -0.7635   0.3183   -0.81   0.4200
treatment  -0.9627   0.2760  -1.5036  -0.4218   -3.49   0.0005
```

$(-3.49)^2 = 12.18$

Recall: square of normal = chi-squared(1)

CHL 5225 H Crossover Trials

Binary Outcome

	(outcome period 1, outcome period 2)					
Sequence	(0,0)	(0,1)	(1,0)	(1,1)	Total	
1 (1,2)	n_{11}	n_{12}	n_{13}	n_{14}		n_{1+}
2 (2,1)	n_{21}	n_{22}	n_{23}	n_{24}		n_{2+}
Total		n_{+2}	n_{+3}			n_{++}

$$X_1^2 = \frac{n_{++}(n_{12}n_{23} - n_{13}n_{22})^2}{n_{1+}n_{2+}n_{+2}n_{+3}}$$

$$X_{c1}^2 = \frac{n_{++}(|n_{12}n_{23} - n_{13}n_{22}| - n_{++}/2)^2}{n_{1+}n_{2+}n_{+2}n_{+3}}$$

$$X_{LR}^2 = 2\sum_{i=1}^{2}\sum_{j=2}^{3} n_{ij}\log\left(n_{ij}n_{++}/(n_{+j}n_{1+})\right)$$

These are two-sided tests

Reject at two-sided, level 0.05 if test statistic exceeds 3.84

Reject at one-sided, level 0.05 if test statistic exceeds 2.72 and observe treatment effect in appropriate direction

CHL 5225 H Crossover Trials

2x2 Cluster Crossover Trial

Sequence	Cluster	Period 1	Period 2
1 (Trt 1→Trt 2)	1	Trt 1 (n_{11})	Trt 2 (n_{12})
	2	Trt 1 (n_{21})	Trt 2 (n_{22})
	3	Trt 1 (n_{31})	Trt 2 (n_{32})
	4	Trt 1 (n_{41})	Trt 2 (n_{42})
	5	Trt 1 (n_{51})	Trt 2 (n_{52})
	6	Trt 1 (n_{61})	Trt 2 (n_{62})
2 (Trt 2→Trt 1)	7	Trt 2 (n_{71})	Trt 1 (n_{72})
	8	Trt 2 (n_{81})	Trt 1 (n_{82})
	9	Trt 2 (n_{91})	Trt 1 (n_{92})
	10	Trt 2 ($n_{10,1}$)	Trt 1 ($n_{10,2}$)
	11	Trt 2 ($n_{11,1}$)	Trt 1 ($n_{11,2}$)
	12	Trt 2 ($n_{12,1}$)	Trt 1 ($n_{12,2}$)

Assume that $n_{ij} = m$, and that within a cluster the patients in Period 1 are different from the patients in Period 2

CHL 5225 H Crossover Trials

2x2 Cluster Crossover Trial – sample size for continuous outcome

$$N = \left\{ \frac{2(z_{1-\alpha/2} + z_{1-\beta})\sigma}{\delta} \right\}^2 \{1 + (m-1)\rho - m\eta\}$$

N = total number of patients required

σ = between patient variance, within a cluster

δ = smallest clinically important difference

ρ = ICC for 2 patients from the same cluster in the same period

η = ICC for 2 patients from the same cluster in different periods

$$c = N/(pm) = N/(2m)$$

c = total number of clusters
m = number of patients per period, per cluster
p = number of periods

CHL 5225 H Crossover Trials

2x2 Cluster Crossover Trial – sample size for binary outcome

$$N = 2\left\{ \frac{(z_{1-\alpha/2} + z_{1-\beta})}{\pi_1 - \pi_2} \right\}^2 \{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)\}\{1 + (m-1)\rho - m\eta\}$$

π_1 and π_2 are the probabilities of the outcome on Treatment 1 and Treatment 2, respectively, under the alternative hypothesis

That is, $\pi_1 - \pi_2$ is the smallest clinically important difference

Giraudeau *et al. Statist Med* 2008; **27**(27):5578–5585
Rietbergen C. *J of Educ and Behav Statistics* 2011; **36**(4):472-490

CHL 5225 H Crossover Trials

PADIT Cluster Crossover Design

High risk patients undergoing arrhythmia device procedures

Treatment 1 (Control): single dose of preoperative cefazolin

Treatment 2 (Intervention): single dose of preoperative cefazolin
plus: single dose preoperative of vancomycin
plus: intraoperative wound pocket wash
plus: postoperative oral cephalexin or cephadroxil

The primary outcome of the trial is admission to hospital for proven device or pocket infection

Six-month periods

Connolly J. *et al Canadian J of Cardiology* 2013; **29**(6):652-658

CHL 5225 H Crossover Trials

PADIT Cluster Crossover Design

$m = 100$	$\alpha = 0.05$	$\pi_1 = 0.02$
$\rho = 0.015$	$\beta = 0.2$	$\pi_2 = 0.013$
$\eta = 0.015$		$\pi_2 - \pi_1 = 0.007$

$$N = 2\left\{\frac{(z_{1-\alpha/2} + z_{1-\beta})}{\pi_1 - \pi_2}\right\}^2 \{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)\}\{1 + (m-1)\rho - m\eta\}$$

$$N = 2\left\{\frac{(1.960 + 0.8416)}{0.007}\right\}^2 \{0.02(0.98) + 0.013(0.987)\}\{1 - 0.015\}$$

$$= 10{,}661$$

$c = N/(2m) = 10661/(2x100) \simeq 54$, assuming 2x2 design

CHL 5225 H Crossover Trials

PADIT Cluster Crossover Design

Sequence	Period 1	Period 2
1→2	Trt 1 Clusters 1 to 28 2800 patients	Trt 2 Clusters 1 to 28 2800 patients
2→1	Trt 2 Clusters 29 to 56 2800 patients	Trt 1 Clusters 29 to 56 2800 patients

CHL 5225 H Crossover Trials

PADIT Cluster Crossover Design

Consider 4-sequence→ 4-period design

1→2→1→2

2→1→2→1

1→2→2→1

2→1→1→2

$$c = N/(pm) = 10661/(4x100) \simeq 27,$$

CHL 5225 H Crossover Trials

PADIT Cluster Crossover Design

Sequence	Period 1	Period 2	Period 3	Period 4
1→2→1→2	Trt 1 Clusters 1 to 7 700 patients	Trt 2 Clusters 1 to 7 700 patients	Trt 1 Clusters 1 to 7 700 patients	Trt 2 Clusters 1 to 7 700 patients
2→1→2→1	Trt 2 Clusters 8 to 14 700 patients	Trt 1 Clusters 8 to 14 700 patients	Trt 2 Clusters 8 to 14 700 patients	Trt 1 Clusters 8 to 14 700 patients
1→2→2→1	Trt 1 Clusters 15 to 21 700 patients	Trt 2 Clusters 15 to 21 700 patients	Trt 2 Clusters 15 to 21 700 patients	Trt 1 Clusters 15 to 21 700 patients
2→1→1→2	Trt 2 Clusters 22 to 28 700 patients	Trt 1 Clusters 22 to 28 700 patients	Trt 1 Clusters 22 to 28 700 patients	Trt 2 Clusters 22 to 28 700 patients

CHL 5225 H Crossover Trials

Cluster Crossover Trial – analysis for continuous outcome

$$y_{ijk} = \alpha_j + \beta x_{ij} + \mu_i + \upsilon_{ij} + e_{ijk}$$

$i = 1, \ldots \#\text{clusters}\ (c)$
$j = 1, \ldots \#\text{periods}\ (p)$
$k = 1, \ldots \#\ patients$

$$\mu_i \sim N(0, \sigma_\mu^2); \quad \upsilon_{ij} \sim N(0, \sigma_\upsilon^2); \quad e_{ijk} \sim N(0, \sigma^2)$$

$x_{ij} = 1$ if cluster i receives treatment 2 during peiod j
$= 0$ if cluster i receives treatment 1 during peiod j

CHL 5225 H Crossover Trials

Cluster Crossover Trial – analysis for binary outcome

$$\text{logit}(\pi_{ij}) = \alpha_j + \beta x_{ij} + \mu_i + \upsilon_{ij}$$

$i = 1, \ldots \#\text{clusters}\ (c)$

$j = 1, \ldots \#\text{periods}\ (p)$

$\pi_{ij} = \text{prob. of outcome for a patient}$
from cluster i during period j

$$\mu_i \sim N(0, \sigma_\mu^2); \quad \upsilon_{ij} \sim N(0, \sigma_\upsilon^2);$$

$x_{ij} = 1$ if cluster i receives treatment 2 during peiod j
$= 0$ if cluster i receives treatment 1 during peiod j

CHL 5225 H Crossover Trials

Assignment:

First line of data:

1, 82.715348081, 67.856553121, 1, 1, 1, 1