Crossover Trials

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Motivating Example

Let's suppose we have a RCT with two treatments (A and B). A group of *n* subjects are administered treatment A while another group of *m* subjects are administered treatment B. This simple and traditional design is called a *parallel design*.

What if group B (or group A) has a disproportionate number of subjects that have characteristics that may alter the results of the trial?

In other words, how do we account for differences in how certain subjects react to specific treatments?

One possible method is using a *crossover design*.

Introduction to the Method

Main Idea

- The **crossover design** is a repeated measures design that allows you to administer all treatments to each subject.
- The subject is used as their own control.
- This allows for fewer subjects while still maintaining statistical power.
- This method helps eliminate some sort of bias in results that comes with subjects having different characteristics.

Design Types

- Sequence: Order of the treatment administration in the experiment.
- Period: Time of the treatment given.
- Treatment: Call A and B.
- The simplest design is as follows…

	Period 1	Period 2
Sequence AB	A	B
Sequence BA	B	A

Each subject is randomly assigned to a sequence group.

Other Design Types

Multiple treatments, periods and different sequences of treatments are all acceptable!

	Period 1	Period 2	…	Period k
Sequence 1	A	B	…	*j*
Sequence 2	B	C	…	*j*+1
…	…	…	…	…
Sequence I	…	…	…	…

For treatments A, B, C, …, *j*

Uniformity

If each treatment appears the same number of times within each sequence, we call this **uniform within sequences**.

	Period 1	Period 2	Period 3	Period 4
Sequence ABAB	A	B	A	B
Sequence ABBA	A	B	B	A

If each treatment appears the same number of times within each period, we call this **uniform within period**.

	Period 1	Period 2	Period 3
Sequence ABA	A	B	A
Sequence BAB	B	A	B

Uniform Crossover Design

	Design 1	Design 2
Sequence AB	A	B
Sequence BA	B	A

A **uniform crossover design** is one that is uniform across sequences and designs. This is the preferred design when using the crossover method.

Balance

In a **balanced design,** each treatment precedes every other treatment the same number of times. In a **strongly balanced design**, each treatment precedes every other treatment the same number of times, *including itself*.

	Period 1	Period 2	Period 3	Period 4	Period 5
Sequence 1	A	B	C	D	D
Sequence 2	B	D	A	C	C
Sequence 3	C	A	D	B	B
Sequence 4	D	C	B	A	A

Each subject receives each treatment and all subjects participate in each period.

Best Design…

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	B	A
Sequence 2	B	A	A	B
Sequence 3	A	A	B	B
Sequence 4	B	B	A	A

Strongly balanced and uniform crossover design. This helps account for the first-order carryover effect.

Notice every person participates in each period and receives each treatment *the same number of times*.

Model

$$Y_{ijkl} = \mu + \delta_l + \beta_{i(l)} + \alpha_j + \gamma_k + \alpha\gamma_{jk} + \varepsilon_{ijkl}$$

Y_{ijkl}	The response due to subject *i*, treatment *j*, period *k* and sequence *l*.
μ	Overall mean
δ_l	Fixed effect due to subject *i* nested within sequence *l*.
$\beta_{i(l)}$	Random effect due to subject *i* nested within sequence *l*.
α_j	Fixed effect due to treatment *j*.
γ_k	Fixed effect due to period *k*.
$\alpha\gamma_{jk}$	Fixed interaction effect due to treatment *j* and period *k*.

Random Assumptions… (pun intended)

$\beta_{i(l)}$ Are independent and approximately normal.

ε_{ijkl} Also independent and approximately normal.

These two components are also independent of each other.

Disadvantages

Main disadvantage is the *carryover effect.* This is described as the confounding that comes with administering one treatment first followed by another.

In other words, measurements taken after treatment B could actually be the result of treatment A.

In an education setting, this is often a major problem.

How do we fix this?

Washout periods are lengthy amounts of time between treatments that allow subjects to be "washed out" of the previous treatment's effects. This helps ensure that the previous treatment will not alter the patient's ability to respond to the second treatment as they normally would.

This amount of time (in a pharmaceutical situation) is typically determined by a multiple of the half-life of the pharmaceutical product.

A strongly balanced design is also used to help with the *carryover effect.*

Disadvantages

This design type should **not** be used when testing for cures. This design must be used for chronic and stable conditions.

> If treatment A cures the condition, there would be no use for treatment B. We would never actually know the usefulness of treatment B.

If there are significant carryover effects, even with lengthy washout periods, it is best to use a different design.

> "It is much more prudent to address a problem *a priori* by using a proper design rather than *a posteriori* by applying a statistical analysis that may require unreasonable assumptions and/or perform unsatisfactorily."

Application

This example is taken from Example 3.1 from Senn's book (Senn S. Cross-over Trials in Clinical Research, Chichester, England: John Wiley & Sons, 1993).

- A study was conducted comparing the effectiveness of two bronchodilators, formoterol and salbutamol, in the treatment of childhood asthma.
- A total of 13 children are recruited for an AB/BA crossover design. A random sample of 7 of the children are assigned to the treatment sequence for/sal, receiving a dose of formoterol upon an initial visit ("period 1") and then a dose of salbutamol upon a later visit ("period 2"). The other 6 children are assigned to the sequence sal/for, receiving the treatments in the reverse order but otherwise in a similar manner.
- Periods 1 and 2 are sufficiently spaced so that no carryover effects are suspected.
- After a child inhales a dose of a bronchodilator, peak expiratory flow (PEF) is measured. Higher PEF indicates greater effectiveness.
- The data are assumed to be approximately normally distributed.

SAS Code – (by hand method)

Published on *STAT 509* (https://onlinecourses.science.psu.edu/stat509)

```
data asthma2;
    input patient sequence $ salbutamol formoterol;
    cards;
    01   FS   270   310
    02   SF   370   385
    03   SF   310   400
    04   FS   260   310
    05   SF   380   410
    06   FS   300   370
    07   FS   390   410
    08   SF   290   320
    09   FS   210   250
    10   FS   350   380
    11   SF   260   340
    12   SF    90   220
    13   FS   365   330
    ;
run;
```

```
/*add a diff column*/
data asthmadiff; set asthma2;
   if sequence = 'FS' then diff = 0.5 * (formoterol - salbutamol);
   if sequence = 'SF' then diff = 0.5 * (salbutamol - formoterol);
run;
/*Sort the data in sequence order*/
proc sort data = asthmadiff;
   by sequence;
run;
/*Gives descriptive statistics and plots*/
proc univariate data = asthmadiff normal plot;
   by sequence;
   var diff;
   title2 'Descriptive Statistics and Graphics for Treatment Difference';
run;
/*perform a t-test to test significance of the differences of means*/
proc ttest data = asthmadiff;
   class sequence;
   var diff;
   title2 'Parametric Analysis';
run;
```

Results

sequence	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
FS		15.3571	0.1119	30.6024	16.4841	10.6223	36.2991
SF		-31.2500	-54.7014	-7.7986	22.3467	13.9490	54.8078
Diff (1-2)	Pooled	46.6071	22.8881	70.3262	19.3702	13.7217	32.8882
Diff (1-2)	Satterthwaite	46.6071	21.6585	71.5558			

Method	Variances	DF	t Value	Pr > |t|
Pooled	Equal	11	4.32	0.0012
Satterthwaite	Unequal	9.1017	4.22	0.0022

SAS Code – (function method)

https://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_ttest_sect012.htm

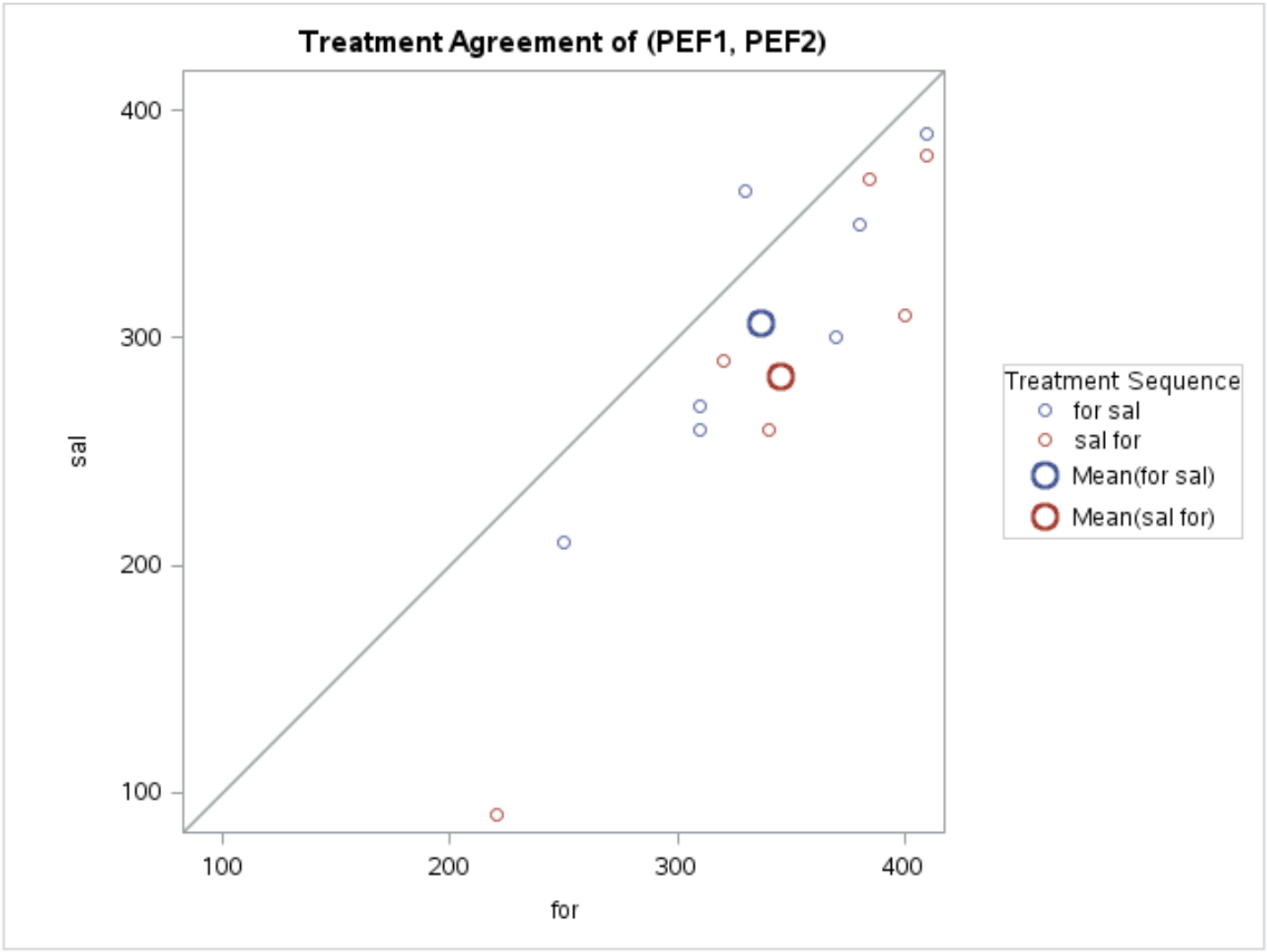
```
/* SAS example 92.4 */

data asthma;
     input Drug1 $ Drug2 $ PEF1 PEF2 @@;
     datalines;
   for sal 310 270   for sal 310 260  for sal 370 300
   for sal 410 390   for sal 250 210  for sal 380 350
   for sal 330 365
   sal for 370 385   sal for 310 400  sal for 380 410
   sal for 290 320   sal for 260 340  sal for 90  220
   ;
run;
proc ttest data = asthma plots = interval;
      var PEF1 PEF2 / crossover = (Drug1 Drug2);
run;
```

Results

Sequence	Treatment	Period	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
1	for	1		337.1	287.4	386.9	53.7631	34.6446	118.4
2	for	2		345.8	271.4	420.2	70.8814	44.2447	173.8
2	sal	1		283.3	172.7	393.9	105.4	65.7841	258.5
1	sal	2		306.4	246.6	366.3	64.7247	41.7082	142.5
1	Diff (1-2)			30.7143	0.2238	61.2048	32.9682	21.2445	72.5982
2	Diff (1-2)			62.5000	15.5972	109.4	44.6934	27.8980	109.6
Both	Diff (1-2)		Pooled	46.6071	22.8881	70.3262	19.3702	13.7217	32.8882
Both	Diff (1-2)		Satterthwaite	46.6071	21.6585	71.5558			
Both		Diff (1-2)	Pooled	-15.8929	-39.6119	7.8262	19.3702	13.7217	32.8882
Both		Diff (1-2)	Satterthwaite	-15.8929	-40.8415	9.0558			

Treatment	Period	Method	Variances	DF	t Value	Pr > |t|
Diff (1-2)		Pooled	Equal	11	4.32	0.0012
Diff (1-2)		Satterthwaite	Unequal	9.1017	4.22	0.0022
	Diff (1-2)	Pooled	Equal	11	-1.47	0.1683
	Diff (1-2)	Satterthwaite	Unequal	9.1017	-1.44	0.1838

1


Treatment Agreement of (PEF1, PEF2)
400
300
200
100
sal
100
200
300
400
for
Treatment Sequence
for sal
sal for
Mean(for sal)
Mean(sal for)

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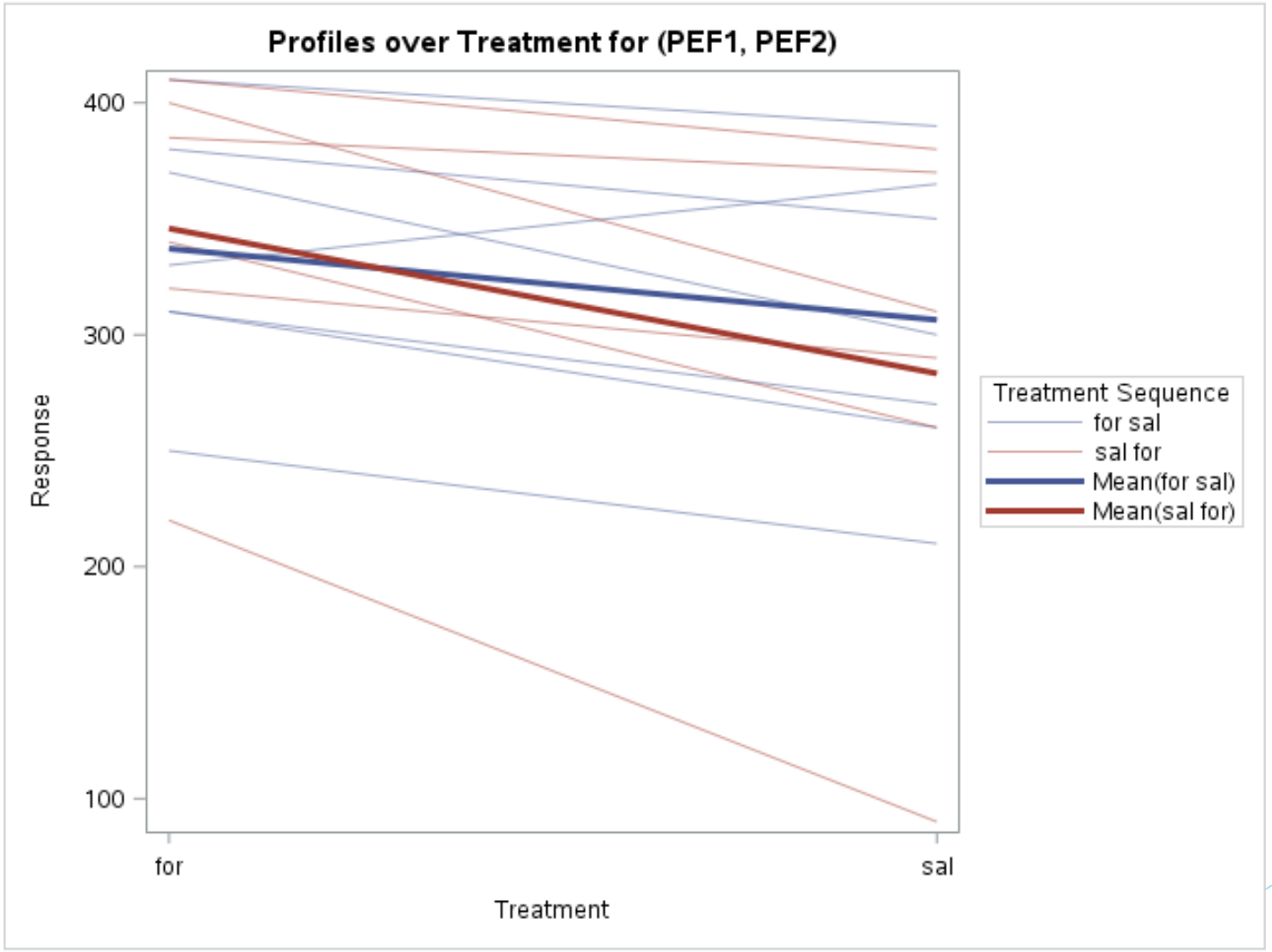
1 Christina stevens, 2/27/2016


Profiles over Treatment for (PEF1, PEF2)
400
300
200
100
Response
for
sal
Treatment
Treatment Sequence
for sal
sal for
Mean(for sal)
Mean(sal for)

Conclusion

- Both versions of code yield same results.
- There is a significant difference between the means of formoterol and salbutamol. We are 95% confident that the difference in the means between the two treatments is between 22.9 and 70.3 PEF units.

Other Functions in SAS and R

- SAS
  - PROC MIXED – used when analysis involves a mixed effects linear model and a continuous outcome
  - PROC GENMOD – used when analysis involves generalized estimating equations and a binary outcome
- R
  - Crossover package: provides more than two hundred cross-over designs from literature, a search algorithm to find efficient cross-over designs for various models and a graphical user interface to find/generate appropriate designs

References

- Senn S. Cross-over Trials in Clinical Research, Chichester, England: John Wiley & Sons, 1993
- Lesson 15: Crossover Designs. (n.d.). Retrieved February 22, 2016, from https://onlinecourses.science.psu.edu/stat509/book/export/html/123
- Matthews, J. N. (2006). Introduction to Randomized Controlled Clinical Trials (2nd ed., Chapman & Hall/CRC Texts in Statistical Science). Chapman & Hall/CRC.