Understanding Crossover Designs

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Why split the subjects into two groups and cross the treatments over?

For a very good reason: you get the same confidence interval for the treatment effect with one quarter the number of subjects as in a fully controlled design, provided there are no practice and carry-over effects. For such a big saving in time and expense, always consider a crossover before a fully controlled study

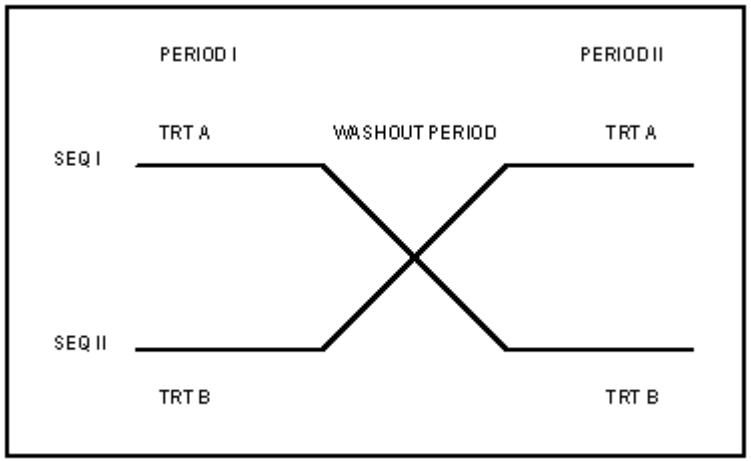


Figure 1. Illustration of a 2 * 2 crossover study design

"The intuitive appeal of having each subject serve as his or her own control has made the crossover study one of the most popular experimental strategies since the infancy of formal experimental design. Frequent misapplications of the design in clinical experiments, and frequent misanalyses of the data, motivated the Biometric and Epidemiological Methodology Advisory Committee to the U.S. Food and Drug Administration to recommend in June of 1977 that, in effect, the crossover design be avoided in comparative clinical studies except in the rarest instances." Fleiss [3, p. 263]

Despite the appeal of having each subject serve as his own control, crossover studies have substantial weaknesses, as well, even beyond the possibility of carryover effects mentioned earlier. Because subjects receive both treatments, crossover studies requires subjects to be available for twice as long as would be necessary for a parallel groups study and perhaps even longer, if a washout period is required between treatments. Acute problems might be gone before the second treatment is applied. A washout period between the two treatments might minimize the effects of the carryover, but this will not be feasible for treatments like fat soluble vitamin supplements that can persist in the body for months.

On the other hand, some features of the crossover may make the design preferable to a parallel groups study. In certain cases, volunteers might be willing to participate only if they receive a particular treatment. The crossover insures that each subject will receive both treatments.

A model proposed by Grizzle (1965)

$$Y_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{trt}_{ij} + e_{ij}$$

where Y_{ij} is the response of subject i at time j, and time_{ij} and trt_{ij} are the values of the time and treatment variable associated with Y_{ij}.

$$Y_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{trt}_{ij} + \beta_3 \text{CO}_{ij} + b_i + w_{ij}$$

where b_i is the subject effect, with

$$\begin{aligned} var\,(b_i) &= \sigma_b^2 \\ var\,(w_{ij}) &= \sigma_w^2 \end{aligned}$$

If there is a carryover of the effect of treatment from period 1 to period 2, we need to define a new indicator variable:

$$CO_{ij} = \begin{array}{l} 1, \text{if } T \text{ given in the previous period;} \\ 0, \text{otherwise.} \end{array}$$

This indicator variable will equal 1 only in the second period for the group assigned to T → P.

id	time	trt	co	y
1	1	1	0	24
1	2	2	0	5
2	1	1	0	23
2	2	2	0	8
3	1	1	0	19
3	2	2	0	3
4	1	1	0	26
4	2	2	0	8
5	1	1	0	16
5	2	2	0	3
6	1	2	0	2
6	2	1	1	18
7	1	2	0	8
7	2	1	1	29
8	1	2	0	5
8	2	1	1	26
9	1	2	0	6
9	2	1	1	28
10	1	2	0	4
10	2	1	1	19

SAS Code for the Grizzle Model

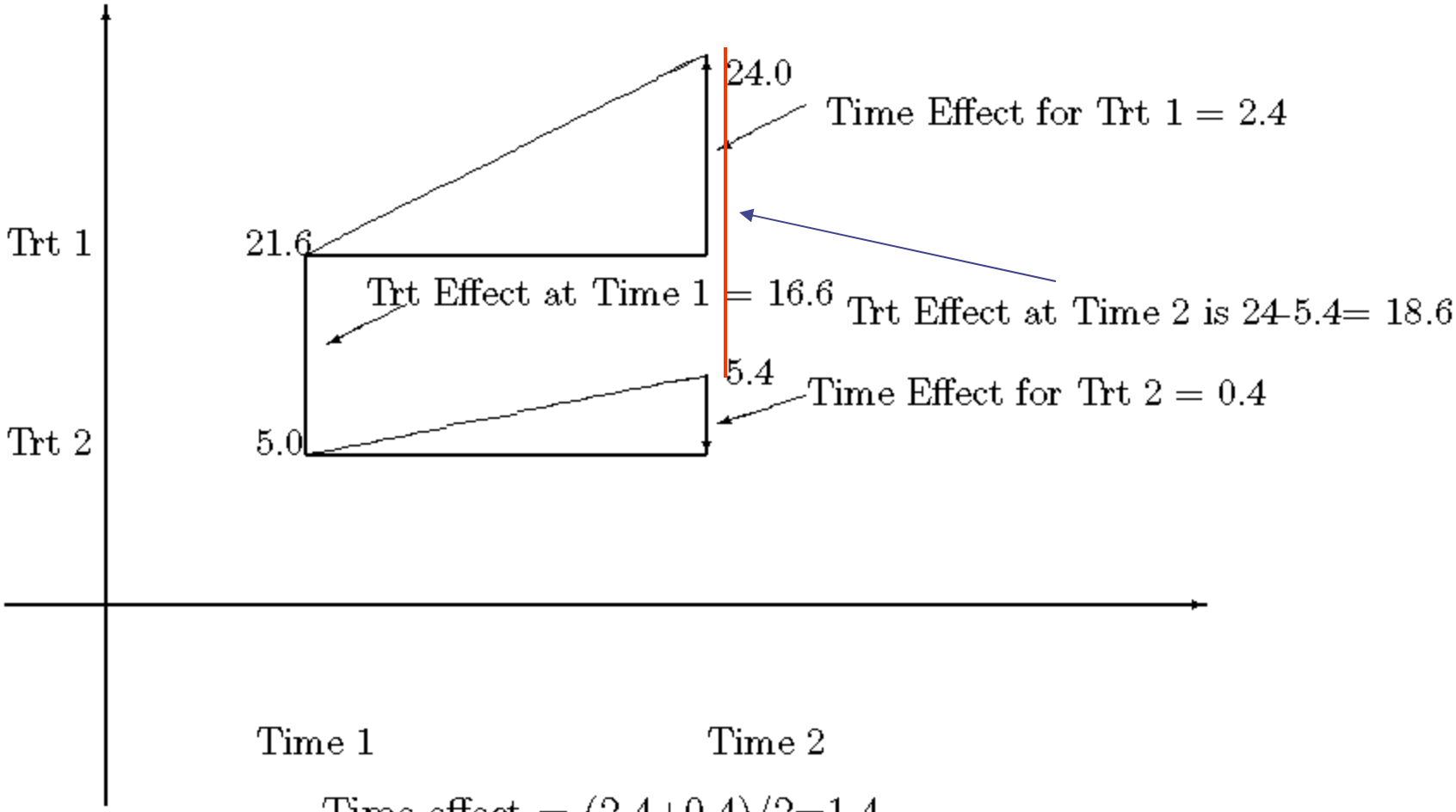
No Carryover Effect

```
proc mixed;
class id time trt;
model y=time trt /s chisq;
repeated time / type=un subject=id r;
run;
```

$$Y_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{trt}_{ij} + e_{ij}$$

Solution for Fixed Effects

Effect	time	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			5.9000	1.2062	9	4.89	0.0009
trt		1	17.6000	0.9000	8	19.56	<.0001
trt		2	0	.	.	.	.
time	1		-1.4000	0.9000	8	-1.56	0.1584
time	2		0	.	.	.	.



Time effect = (2.4+0.4)/2=1.4.

Trt effect = (16.6+18.6)/2=17.6.

SAS Code for the Grizzle Model

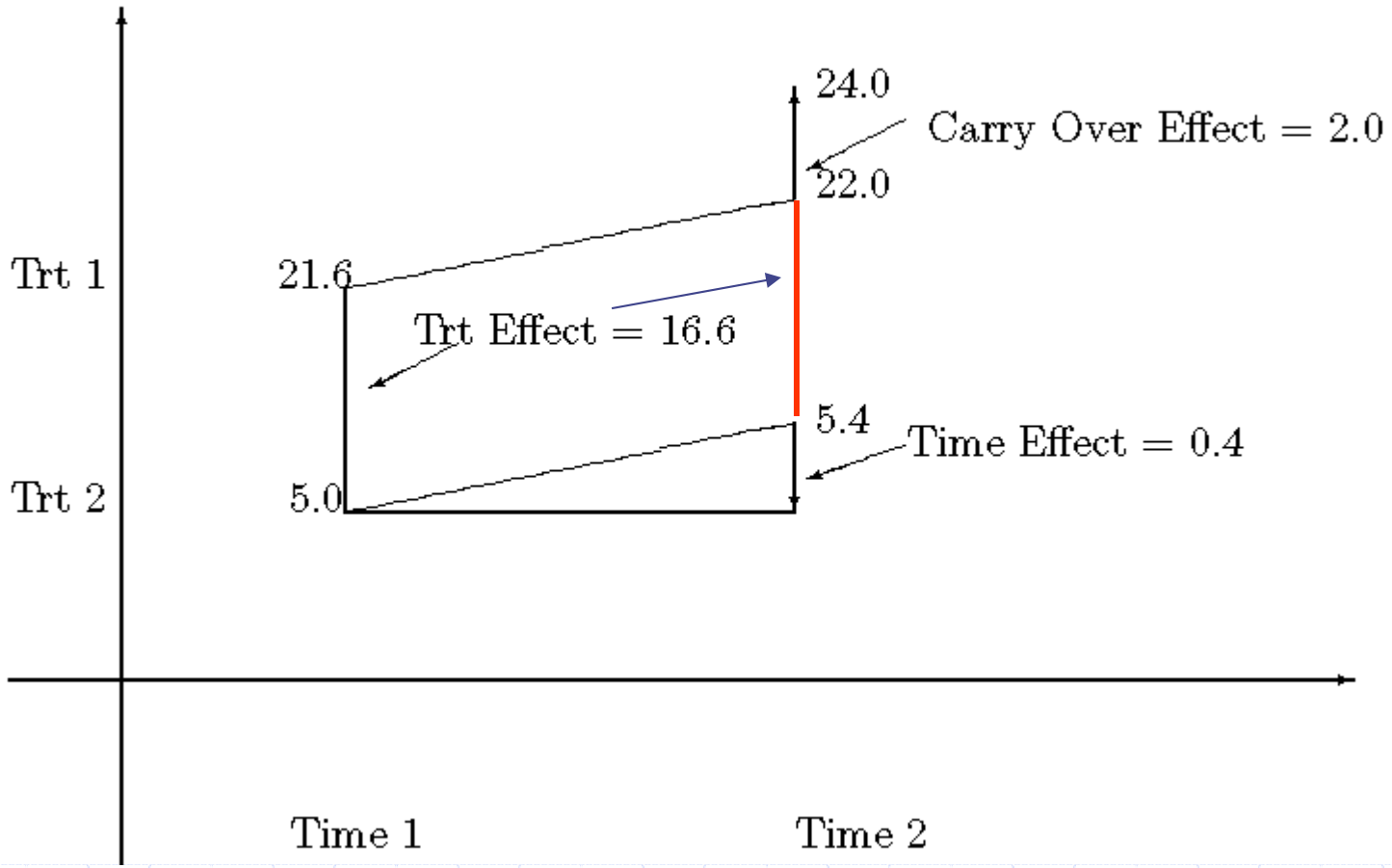
With Carryover Effect

```
proc mixed;
class id time trt co;
model y=time trt co /s chisq;
repeated time / type=un subject=id r;
run;
```

$$Y_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{trt}_{ij} + \beta_3 \text{CO}_{ij} + b_i + w_{ij}$$

Solution for Fixed Effects

Effect	time	trt	co	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				7.4000	3.4504	9	2.14	0.0606
trt		1		16.6000	2.3259	7	7.14	0.0002
trt		2		0	.	.	.	.
time	1			-0.4000	2.3259	7	-0.17	0.8683
time	2			0	.	.	.	.
co			0	-2.0000	4.2895	4	-0.47	0.6653
co			1	0	.	.	.	.


24.0
Carry Over Effect = 2.0
22.0
Trt 1
21.6
Trt Effect = 16.6
5.4
Time Effect = 0.4
Trt 2
5.0
Time 1
Time 2

Dilemma: Choice of an estimator for treatment effect is between an efficient but potentially biased estimator (using within-subject comparisons) and an unbiased but inefficient estimator (using between-subject comparisons).

This problem is an intractable feature of the simple crossover design. Thus, it should be used only when carryover is biologically implausible.

Carryover can often be avoided by having a sufficiently long wash-out time between the two periods.

Summary

When the crossover design is used, it is important to avoid carryover. Designing a crossover study requires knowledge and consideration of the disease and the likely effects of treatment:

- The disease should be chronic and stable
- The effects of treatment should develop fully within the treatment period

Washout periods should be sufficiently long for complete reversibility of treatment effect. The crossover design may be useful for demonstrating the bio-equivalence of two formulations of the same drug.

References

1.Grizzle JE. The two-period change-over design and its use in clinical trials. Biometrics 21, 467-480 (1965).

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6.Milliken GA, Johnson DE. Analysis of Messy Data. Van Nostrand Reinhold Co., New York (1984).