

Implementing Crossover Design in Drug Abuse Potential Studies

-- Issues and Strategies

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Outline

- ◆ Introduce for drug abuse potential clinical trials
- ◆ Reasons of using a crossover design
- ◆ Issues and Strategies
- ◆ Concluding Remarks

Regarding Scheduling Decisions

- ◆ The decision to schedule or not schedule a drug is based on a comprehensive evaluation of all data from biochemical / binding studies, from animal behavioral studies, from adverse events observed in clinical efficacy studies, as well as from data from human abuse potential and clinical studies.
- ◆ The Controlled Substance Staff (CSS) take all information available, consider the total impact, and make a recommendation from there.
- ◆ A single study (or a single endpoint) can play a large role in the recommendation, but the final decision depends on the total picture from all the data.

Objectives of Drug Abuse Potential Study

- ◆ Provide unique information on the relative abuse potential of new drugs in humans
- ◆ Predict the likelihood of abuse by recreational drug abusers
- ◆ Predict the extent of drug diversion & illicit street sales if the new drug becomes available to the drug abuse community
- ◆ Provide information for scheduling a drug

Outcome Measures:

Most directly related to likelihood of abuse

- ◆ Ratings of liking
 - “do you like the drug you are feeling now?”,
 - “good effects,” “bad effects”
- ◆ Disposition to take the drug again
 - “degree to which you would like to take the drug again,”
 - “estimate of street value of the drug,” “estimate of amount of money you would personally be willing to pay for the drug.”
- ◆ Street Value & Drug vs. Money choice behavior
 - Relatively new innovation that puts a dollar value on the drug experience.
 - **However, the test is known to the CSS to be an un-validated measure and should not be included in the statistical analysis.**

Treatments in the Trial

- ◆ Placebo
- ◆ Multiple doses of the test drug (usually three)
- ◆ Multiple doses of the positive control drug
- ◆ Sometimes more than one positive control drug with multiple doses
- ◆ The total number of treatments in the study is large. It could be as large as eight.

Assessment Criteria

To claim that there is no potential for abuse liability of a new drug, for each primary variable the sponsor needs to show that

- ◆ The positive control drug has statistically larger mean response than placebo. (validating the trial)
- ◆ All doses of the new drug have statistically lower mean response than each validated dose of the positive control drug.
- ◆ All doses of the new drug are shown to be of no higher abuse potential than placebo. (an example of demonstrating this would be to show that each mean response is no more than double the mean response of placebo)

Reasons for Using a Crossover Design for Drug Abuse Potential Studies

- ◆ Many treatments are needed in the study.
- ◆ There is large between subject variability in endpoint measurements based on self-evaluated responses.
- ◆ Difficulty of recruiting appropriate study subjects – healthy recreational drug abusers

Advantages of Using a Crossover Design

- ◆ It could yield a more efficient comparison of treatments than a parallel design, i.e., fewer experimental units might be required in the crossover design in order to attain the same level of statistical power, precision, and efficiency as a parallel design.
- ◆ Intuitively, this seems reasonable because each experimental unit serves as its own matched control.

See Vonesh and Chinchilli, 1997, Design and analysis of Cross-Over Trials.

Study Model

Commonly used study model is as follows:

Response = period + sequence + treatment
+ first-order-carryover

Random subject(sequence) or

Response = period + treatment + first-order-
carryover

Random subject

Here we assume that first-order-carryover effects from one treatment to any other treatments are constant, and there is no direct-by-carryover interaction.

Commonly used design

Williams Design (1949)

6x6

A	F	B	E	C	D
B	A	C	F	D	E
C	B	D	A	E	F
D	C	E	B	F	A
E	D	F	C	A	B
F	E	A	D	B	C

5x5

A	E	B	D	C	C	D	B	E	A
B	A	C	E	D	D	E	C	A	B
C	B	D	A	E	E	A	D	B	C
D	C	E	B	A	A	B	E	C	D
E	D	A	C	B	B	C	A	D	E

❖ Advantage:

1. It is a variance-balanced design. The balance can be achieved by a single Latin square for an even number of treatments or two particular Latin squares for an odd number of treatments.
2. If the first-order carryover effects from one treatment to any other treatments are constant, the design balances the first-order carryover effects.

❖ Disadvantage:

Insufficient number of degrees of freedom to assess direct-by-carryover interaction using a single Williams square design.

Adding One More Placebo

- ◆ One possible way to resolve the problem with single square Williams design is to include one more placebo in the study.
- ◆ We may pre-specify one of the placebos to be used in the comparison with the test drug and the positive control drug (keep variance balance)
- ◆ The additional placebo response can be used for sensitivity analysis and use to assess carryover effects.
- ◆ If one wants to increase the precision of the estimation of the placebo effect, one may combine two placebo responses by averaging them within subjects.

Concern with Dropouts

- ◆ For an inpatient study, dropouts rarely occur. Dropouts may occur in outpatient studies.
- ◆ Recent practice:
If a subject discontinues the study, to keep the balance of the Williams square design the same sequence is assigned to a new subject.

Criticism:
Affects blinding

A Strategy for Avoiding Unblinding

- ◆ The Sponsor should ship the study medication in a small package for each sequence (randomly assign a code to each sequence). In the package, separate treatments into periods. With a double-dummy design, neither the investigator nor the study subjects would know which drug was assigned in a particular drug session.
- ◆ The random code of a sequence may help the Sponsor to assign the same sequence of drug sessions to a subject who replaces the non-completer. In such a way, the Sponsor may not only keep balance of the design for the study but also keep the blinding.

Completer or ITT Analysis?

- ◆ The drug abuse potential studies are very different from any efficacy study or general safety studies. The objective of the study is to accurately assess abuse liability of a new drug. The analysis do not have to be based on ITT population.
- ◆ In order to keep the good properties of the Williams square design, completer analysis is strongly recommended for drug abuse potential studies.
- ◆ We also request sponsors to document and report the incomplete data from dropouts to FDA for review.

Washout Period and Duration of the Study

- ◆ Drug abuse potential study is a study with a single dose administration.
- ◆ The duration of an inpatient study equals one day for each treatment plus days between treatments based on the washout periods.
- ◆ Insufficient washout period results in carryover effects and complicates assessing treatment differences.
- ◆ A frequent recommendation for the washout period of a crossover design study is *at least 5 times the maximum $T_{1/2}$ of the treatments in the study* in PK studies.

Proposed New Design

- ◆ For illustration purpose, suppose the original used Latin square is

A E B D C where A: Placebo

B A C E D

B: Low dose of the positive control drug

C B D A E

C: High dose of the positive control drug

D C E B A

D: Low dose of the new drug

E D A C B

E: High dose of the new drug

and the positive control drug has a long half life of 19 hours. The adequate washout period is 4 days. The duration of the studies is 17 days ($5 + 3 \times 4$).

Continued ...

A	E	B*	D	C*		A	E	B	P	D	C	P
B*	A	C*	E	D		B	P	A	C	P	E	D
C*	B*	D	A	E	→	C	P	B	P	D	A	E
D	C*	E	B*	A		D	C	P	E	B	P	A
E	D	A	C*	B*		E	D	A	C	P	B	P

where B* represents B followed by a placebo, similarly for C* and C.

- ◆ Since the new drug has a half-life of 9 hours, the study duration based on the new design is 13 days (7+1x6).
- ◆ It should be noticed that responses from placebo after the positive control drug should not be used in analysis due to the carryover effect. The new design can be still analyzed as the 5-treatment, 5-period Latin square design.

A Modified Washout Period

- ◆ When one drug has a much longer $T_{1/2}$ than other drugs in the study, according to the new design, the rule of the washout period can be modified as at least 5 times the second largest $T_{1/2}$ of the treatments in the study.
- ◆ How many placebos are needed to be placed after the treatment with the maximum $T_{1/2}$ depend on the maximum $T_{1/2}$.
- ◆ To use the modified washout period, the sponsor must select study subjects carefully by using qualifying session before treatment sessions to minimize possible placebo effect.

Concluding Remarks

- ◆ Drug abuse potential study has large number of treatments and needs crossover design. Williams square design is highly recommended.
- ◆ We proposed a way to reduce the duration of the study. However, PD effects might be delayed. We suggest using sufficiently long washout period to avoid any carryover effects unless one can assure carryover effects to be first order and constant.
- ◆ We recommend replacement of missing subjects by using the same sequence to retain the good properties of the balanced William square design.

Reference

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