Understanding Crossover Design

In this issue, Hunt, Sanderson, and Ellison (2014) report on a study that used a randomized crossover design with repeated measures. Randomized, controlled crossover experiments are an important research approach in health care. In this column, I will discuss the nature, advantages, and limitations of this design.

What Is a Crossover Design?

The crossover study or trial is a longitudinal study in which participants receive different interventions or an intervention and the control, usually the standard treatment, in a sequence. All participants receive the same number of treatments and participate in the same number of study periods (Polit & Beck, 2014). The simplest model is AB/BA, but it can become complex; for example, ABC/BCA/CBA could be used, as well as other combinations depending on the purpose of the study. The sequencing of treatments is different from a simple experiment, in which one group receives the treatment and another group receives the standard of care treatment. In the case of a simple experiment, researchers try to obtain equivalent groups by using random assignment to groups and sufficient numbers. In a crossover study, each participant also is a control and the randomization determines which treatment each participant receives first.

In the study by Hunt and colleagues (2014), one group received an iPad to log diabetes management activities and the second group used a paper journal for the first 3 months; then they switched approaches for the second 3 months. All participants thus used both approaches. Crossover studies also have been used, for example, to compare high-flow nasal cannulas and conventional oxygen therapy after endotracheal extubation (Rittayamai, Tscheikuna, & Rujiwit, 2014) and alternative methods of alleviating infant pain during heelsticks (Liew et al., 2012). They are popular for drug trials (Mills et al., 2009).

As mentioned, each participant serves as his or her own control. The basic purpose of this type of study is to separate the treatment effect from the period effect (Welleck & Blettner, 2012). The **treatment effect** is the extent of improvement due to the intervention being tested. The **period or order effect** represents the possible influence of the sequence on the intervention’s effectiveness. Perhaps, patients who used the iPad first became accustomed to recording activities on an easy-to-carry device and then did not like the paper journal. This can be compared to the group recording with the paper journal first, becoming accustomed to recording activities, and then changing easily to the iPad. This period effect can be informative for future studies.

Crossover studies usually are restricted to patients with chronic, stable conditions such as diabetes. These conditions will not change frequently or rapidly during the duration of the study, so the effect of the treatment cannot be confused with the effect of the changing condition. In addition, crossover studies generally are limited to alleviating symptoms and not creating cures (Elbourne et al., 2002).

Advantages

The main advantage of the crossover design for a researcher is avoiding the problem of the comparability of groups on confounding variables. Patient variation is removed because participants serve as their own controls. If one group in the study by Hunt and co-authors (2014) by chance contained more people already familiar with iPads, this could have been a confounding variable in a simple experiment. Researchers try to control this with randomization, but there is no guarantee all confounders will be controlled. In a crossover design, this is less of an issue (Sibbald & Roberts, 1998).

This design also requires smaller, more efficient sample sizes. Less numbers are needed to meet the same criteria for reducing Type I and Type II errors. This can be important when study populations are small or contain patients who are severely ill. In this type of design, the power of the statistics used to confirm a treatment effect is higher (Welleck & Blettner, 2012), requiring fewer participants.

Because the participants receive both treatments, researchers also can evaluate them and express preferences for and against particular treatments (Mills et al., 2009). Participants in the study by Hunt and colleagues (2014) were able to tell researchers the food entry section on the iPad application was difficult to use. This allowed developers to modify that function in the future.

Limitations

The main limitation of the crossover design is the **carry-over effect**, in which the effect of one treatment carries over into the next period. To counteract this problem, particularly in drug studies, researchers will have a

Lynne M. Connelly, PhD, RN, is Associate Professor and Director of Nursing, Benedictine College, Atchison, KS. She is Research Editor for MEDSURG Nursing.
wash-out period between treatments in which no treatment is given (Mills et al., 2009). A researcher must know the length of time sufficient for the treatment to be effectively washed out (Welleck & Blettner, 2012). Some researchers use statistics to test for a carry-over effect, but this is controversial (Sibbald & Roberts, 1998). Most experts recommend researchers only use this design if they are confident before the study that no carryover effect will exist after a washout period (Cummings, 2010).

In many types of designs, including the crossover approach, a learning effect can exist. In this case, participants, particularly those new to the treatment, will learn the purpose of the treatment and adapt to it better over time. In the study by Hunt and co-authors (2014), both groups would have become accustomed to logging in their activities during the first 3 months; this behavior could have become normalized and easier over time, possibly creating a carry-over effect for the second period no matter what method of logging was used.

Attrition or the loss of participants from one treatment to the next is another issue. For lost participants, within subject comparisons are impossible. Attrition is particularly important if withdrawing is due to side effects or participants not liking the treatment for some reason (Mills et al., 2009). The numbers of lost participants and the reasons (if known) for the attrition should be reported as was done in the study by Hunt and colleagues (2014).

Crossover designs are used frequently in health care studies and readers should be familiar with the nature of this approach to comparing treatments. As with all designs, they have strengths and limitations. The informed reader can judge the utility of a study’s findings for his or her possible use.

REFERENCES