Chapter 7
Advantages, Disadvantages, and Future Trends on the Use of Design of Experiments in Cross-Over Trials in Nutritional Clinical Investigation

Jose Manuel Miranda
Universidade de Santiago de Compostela, Spain

Alicia del Carmen Mondragon Portocarrero
Universidade de Santiago de Compostela, Spain

Alexandre Lamas Freire
Universidade de Santiago de Compostela, Spain

Carlos Manuel Franco Abuin
Universidade de Santiago de Compostela, Spain

Alberto Cepeda Saez
Universidade de Santiago de Compostela, Spain

ABSTRACT

The use of clinical trials to demonstrate effect of foods consumption on human health has increased significantly in recent years at the global level. As in other areas of human health, some authors choose to use parallel trial designs, while others prefer to use crossover designs for these trials. Because crossover trials have the advantage of reducing the number of subjects needed and the economic cost to be performed, they have many advocates within the scientific community. However, these types of tests also have numerous drawbacks, due to the difficulty of carrying out adequate statistical analyses, the lack of reliable standards adapted to them or confounding factors. In this chapter, the advantages and disadvantages of crossover designs and whether they are a recommended option for human nutrition research are shown. The usefulness of design of experiments coupled to crossover trials, especially when comparing various levels of the dependent variable, are also discussed.

DOI: 10.4018/978-1-7998-1518-1.ch007

INTRODUCTION

Human clinical trials are often designed to assess the effectiveness of an intervention or treatment on human health. Typically, these trials are used to test the efficacy of different therapeutic options in medicine, pharmacology or nutrition. However, in the last decades the use of such trials is increasingly common for the investigation of the effect of other types of habits and interventions on human health, as may be the case with nutrition baseline research. In addition to basic research, one of the most common purposes for conducting nutrition trials is to demonstrate the beneficial effects of a specific food component in order to use this information in the in food labeling. Food products that are labeled with messages related to the promotion of human health are marketed at a price 30–50% higher than their counterparts that cannot use these health claims, and in some cases can reach even more (Miranda et al., 2018). In order to obtain authorization for the use of one of these health claims, it is usually necessary to present a meta-analysis demonstrating the beneficial effects of the food on human health. As an example, in the European Union it is compulsory to include human trials to obtain authorization for the use of health claims in marketing food products (European Food Safety Authority, EFSA, 2011). Following this obligation imposed by the European Union, the number of nutrition-related clinical trials published worldwide increased significantly. As it can be seen in Figure 1, clinical trials related to human nutrition showed gradual growth between 2000 and 2010, which accelerated substantially from that date onwards for both cross-clinical trials and for other types of clinical trials.

Randomized clinical trials are considered the "gold standard" to evaluate therapeutic effectiveness due to its ability to avoid or minimize bias associated with imbalance in potentially confounding variables (Leonard, Lafrenaye & Goffaux, 2012). The most employed randomized clinical trials are the so-called parallel-group trial or design (Harris & Raynor, 2017), in which subjects are randomized to a unique intervention or control group during the entire trial, that occur simultaneously in time. Identical dependent outcome variables are measured in all groups included in the trial, with outcomes compared between groups, or between subjects, with the aim to determine the intervention effectiveness. In contrast, in a so-called crossover design, all subjects receive all levels of the independent variable at some point in the study, but subjects do not receive all levels at the same time (Figure 2). To determine intervention effectiveness, dependent outcome variables are measured for the two levels of the intervention and afterwards, then they are compared within the same subject (Harris & Raynor, 2017).

Although cluster-randomized crossover trials have become a popular tool in nutritional clinical investigation, some important characteristics of this kind of studies have not been clearly standardized for these emergent trials. In many cases, the principles from cluster-randomized trials with parallel design are not easily applied to a crossover setting (Reich, Myers, Obeng, Milstone & Perl, 2012). Additionally, on many occasions, researchers found complications to include crossover trials in systematic reviews and the meta-analysis, required to obtain an authorization for obtaining a health claim (Li, Tsung, Hawkins & Dickersin, 2015). In many published meta-analyses, the authors choose to include the results from crossover trials unfolded as if they become from a parallel design (Reich et al., 2012). A clear example of this difficulty can be seem in a recent meta-analysis (Yan, Guan, Gao, & Peng, 2018) related to omega-3 fatty acids effects and their effect in non-alcoholic fatty liver disease, in with textually excluded "uncontrolled, crossover, cross-sectional, and not reporting outcomes of interest or primary data."

Another crucial point in nutritional trials is that clinical trials are usually designed with the implicit assumption that data analysis will occur only after the trial is completed. While this affirmation is correct in pharmacological trials (volunteers received a treatment in order to treat a pathology), in the case