# A Two-by-two Trial Design and Behavior-treatment interaction

Discovering a new pharmaceutical product or therapy is a process which requires compliance with all Good Clinical Practice (GCP) regulations. However, the complexity of this matter also lies in the fact that **in order to obtain the most productive results, researchers need to integrate the most suitable and bias-free methods**. Thus, the best implementation as well as assessment of the new drug depend on the so called double-blind randomized controlled trials (DBRCTs). These trials are perceived as the gold standard in defining the real drug efficacy and level of treatment effectiveness without patient or doctor bias.

A huge part of the medicine techniques are based on testimonials, common sense and, basically, tradition that is expressed in the form of already established know-hows across time. Occasionally this seems to be working just fine because su**ccessful results and demonstrative cases are present** and at hand. Nevertheless, such "surface" schemes are not always the most yielding sources of information. And when correct information, data, specifics and outcomes play core importance in the creation of a new medical product, **specialists cannot make any sacrifices in terms of adopting research mechanisms**. Unfortunately, there are too many external and internal elements which are risky and might influence the whole course of a specific trial. **Such elements can be gender, social differences, smoking status and even unknown genetic differences.**

Because of this, currently utilized double-blind randomized controlled trials might not be the best ways to evaluate the effects of different factors and behaviors that accompany the study environment and patients too. In attempt to tackle the drawbacks of the DBRCTs, a new trial design has been suggested. It is called the two-by-two trial. According to researchers, **it is simply a necessity for "digesting" just what is needed in order to prove whether a treatment really works**, without

inflicting appearances of effectiveness where actually none of it exists and is, in fact, illusory. In simple words, this study design accounts for behavior-treatment interactions.

The question that may arise here is why acknowledging such interactions is important. By all means, subjects who participate in a trial behave in distinctive, individual and different ways. These behaviors **can have a direct impact on the study itself and the final results**. Such impacts can navigate the study either to a positive or to a negative direction.

As an example that aims to illustrate this more vividly, let's take two individuals who take part in a trial that tests a drug that helps losing weight. One of subjects arrives with the conviction that the medical product works on 100%. The other person, on the contrary, is told that the drug has 40% effect-probability. This makes the latter participant more skeptical and urges him/her to believe that the treatment is not that efficient. What happens next is that the first patient continues to take the drug on regular basis and according to the schedule. The second one, on the other hand, does not follow the treatment regimen systematically and might even miss some doses. Respectively, this will bounce back to the outcomes at the end of the trial. Hence, in one of the cases, the drug will work, while in the other case it will not.

**In order to avoid such outcomes that are the product of patients' behaviors**, the two-by-two randomized controlled trial turns out to be the most useful tool. Here, "instead of patients first being assigned to either the experimental or control groups, they are randomly assigned to either a "high probability of treatment" group or a "low probability of treatment" group. The patients in the high

probability group are then randomly assigned to either the treatment or the control group, giving them a 70 percent chance of receiving the treatment. Patients in the low probability group are also randomly assigned to treatment or control; their likelihood of receiving the treatment is 30 percent. **The patients are then informed of their probability of treatment**." (Chassang S, Snowberg E, Seymour B, Bowles C (2015) Accounting for Behavior in Treatment Effects: New Applications for Blind Trials. PLoS ONE 10(6): e0127227. doi:10.1371/journal.pone.0127227)

Commenting on the nature of this study design in particular, **Caltech's Erik Snowberg, professor of economics and political science**, says that; "Most medical research just wants to know if a drug will work or not. We wanted to go a step further, designing new trials that would take into account the way people behave. As social scientists, we naturally turned to the mathematical tools of formal social science to do this."

**The working characteristics of the new trial outline are due to the fact that it randomizes both the treatment and the probability of the treatment**. This way, researchers are enabled to measure three pivotal aspects, including the effects of the behavior of participants, the effects of the treatment itself and, finally, the effects of the combination between those two, e.g. the interaction between behavior and treatment. Only **when all of these are clearly established, one can comprehend the overall efficacy of the trial process**.

*Originally Posted Here: [https://crotraining.co.uk/a-two-by-two-trial-design-and-behavior-treatment-interaction/](https://crotraining.co.uk/a-two-by-two-trial-design-and-behavior-treatment-interaction/)*