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Randomised controlled trials of factorial design alias on how to speed up research on effectiveness of interventions without compromising its validity

One of the main limitations of randomised controlled trials (RCTs) is that they can answer one question per time. In a classical RCT, one intervention is tested against another in different patients (parallel group design with two arms). It is also possible to compare more than two interventions by increasing the number of arms in the study. However, many more patients would be required to be able to find a statistically significant difference, making such a trial costly and difficult to implement. Traditional research methods generally study the effect of one factor at a time, because it is statistically simpler. However, sometimes, two factors may be interdependent, and it would be more convenient to analyse them using a factorial design. Such a design allows the evaluation of a larger number of factors and whether there is a relationship between factors. In other words it simplifies the process, making research cheaper and faster. However, the factorial studies have to be planned meticulously, as an error in the trial construction can jeopardise the outcome.

There are two main types of variables: independent variables (also called factors), which are variables whose values do not depend on the value of another variable, and dependent variables, whose values depend on the independent variables. When there are multiple independent variables in a single study, it is called a factorial design. A factorial design does not have to have just two independent variables; it can have as many as you want. Such a study design allows us to study the effect of each factor on the dependent variable, as well as the effects of interactions between factors on the dependent variable. Each factor has only two levels in the majority of factorial trials. For example, with two factors, each taking two levels, a factorial experiment would have four treatment combinations in total, and is called a 2 × 2 factorial design.

The main practical advantage of factorial trials is the reduced sample size. In conventional trials, the power to detect treatment differences depends on the number of participants in each group to be compared rather than the total number of participants in the trial. This sample size calculation is based on the assumption that there is no interaction between the interventions, but this is not always the case. In the presence of interactions between interventions, factorial trials have more power to detect the main effects of interventions, requiring smaller sample sizes than conventional RCTs.

The statistical analysis of factorial trials focuses on investigating the main effects and the interaction between the interventions using appropriate regression models. In the regression analyses, the effect of each intervention will be adjusted for the other intervention as well as any necessary covariates, such as the outcome measure for baseline and stratification variables.

Finally, factorial trials would be contraindicated for interventions that could not be used in conjunction with one another, and when the primary interest is in the direct comparison of the two interventions applied individually.

It is easier to understand the concept of factorial design by making a practical example. The purpose of a RCT could be to evaluate the efficacy of different bone augmentation procedures for dehiscence defects at implant placement. The study could be designed as a 3 x 2 factorial RCT (3 x 2 means that there are 3 factors at two levels each). The three factors (treatments or interventions) could be the type of implant used, the bone substitute and the membrane applied. The levels could be represented by two different implant surfaces, two different bony substitutes and two different membranes. In total, eight treatment combinations (2^3) will be applied.

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This study is more efficient than one-factor-at-a-time studies. Furthermore it can highlight interaction effects. For example, a bone substitute can obtain better results when used with a particular membrane and worse results are obtained when used with the other membrane.

One may wonder why such an interesting study design is so uncommon in dentistry. Somebody may think that it is a new study design, but it was actually originally used as early as 1843 in practical agriculture by Sir John Bennet Lawes and Sir Joseph Henry Gilbert of the Rothamsted Experimental Station near London, so why it is so rarely used? This is most likely because it is different from what we are used to dealing with and people sometimes feel unfamiliar with different study designs and prefer to stick to what they are more familiar with. Personally, we are experiencing this problem, not only with potential trial sponsors, but even with ethical committees who are not familiar with the factorial study design and who may oppose inconsistent excuses against them. Needless to say EJOI is open to this type of study design and we shall welcome well-designed trials trying to answer multiple questions using the factorial design.

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