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This Section of *Epidemiology and Psychiatric Sciences* regularly appears in each issue of the Journal to cover methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. The aim of these Editorials is to help developing a more critical attitude towards research findings published in international literature, promoting original research projects with higher methodological standards, and implementing the most relevant results of research in every-day clinical practice.

Corrado Barbui, *Section Editor* and Michele Tansella, *Editor* EPS

What is a factorial trial?

A. Cipriani* and C. Barbui

Department of Community Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy

Randomized controlled trials (RCTs), typically, randomize participants to one of two intervention groups. It has been shown, however, that about 25% of RCTs published in the scientific literature randomize participants to three or more treatment groups. These studies are called 'multi-arm' trials: there may be, for instance, two or more experimental intervention groups with a common control group, or two control intervention groups such as a placebo group and a standard treatment group. A special case of multi-arm studies are factorial trials, which address two or more intervention comparisons carried out simultaneously, using four or more intervention groups.

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Randomized controlled trials (RCTs), typically, randomize participants to one of two intervention groups (Cipriani & Geddes, 2009). It has been shown, however, that about 25% of RCTs published in the scientific literature randomize participants to three or more treatment groups (Chan & Altman, 2005). These studies are called 'multi-arm' trials: there may be, for instance, two or more experimental intervention groups with a common control group, or two control intervention groups such as a placebo group and a standard treatment group. A special case of multi-arm studies are factorial trials, which address two (or more) intervention comparisons carried out simultaneously, using four (or more) intervention groups. Most factorial trials have two 'factors', each of which has two levels (i.e., two possible groups of allocation); these are called 2 × 2 factorial trials. In a hypothetical 2 × 2 factorial trial, participants are randomized to one of four groups: one group receives both treatments A and B (AB), one receives only treatment A (A0), one only treatment B (B0), and the remaining group receives neither treatment A nor B (00) (see Table 1). To preserve blinding, the latter three may be given the corresponding placebos. Occasionally 3 × 2 trials may be encountered, or trials that investigate three, four, or more interventions simultaneously.

When designing a factorial trial, the main intention of researchers is to achieve 'two trials for the price of one'. To do so, an important assumption is that the effects of the different active interventions are independent. In other words, there should be no interaction (no synergy or antagonism) between the treatments. From this point of view, a 2 × 2 factorial trial can be seen as two trials addressing different questions on the same study population. It is important that both parts of the trial are reported as if they were just a two-arm parallel group trial. For this reason, the treatments selected for investigation in a factorial trial should have no known clinical interactions and, perhaps, different mechanisms of action. Consistently, it has been suggested that properly conducted factorial trials may be the best available way to investigate whether an interaction exists between treatments

* Address for correspondence: Dr A. Cipriani, Department of Medicine and Public Health, Section of Psychiatry – University of Verona, Piazzale L.A. Scuro, 10–37134 Verona, Italy.
(Email: andrea.cipriani@univr.it)

Table 1. *In a 2 × 2 factorial design participants are randomly assigned to 1 of 4 groups: one group receives both treatments A and B (AB), one receives only treatment A (A0), one receives only treatment B (B0), and the remaining group receives neither treatment A nor treatment B (00)*

	Randomization of treatment A		
	Yes (A)	No (0)	
Randomization of treatment B			
Yes (B)	Both A and B (AB)	B alone (B0)	All B (AB and B0)
No (0)	A alone (A0)	Neither A nor B (00)	All non-B (A0 and 00)
	All A (AB and A0)	All non-A (B0 and 00)	Analysis 'at the margins'

(McAlister *et al.* 2003). This is an interesting point of increasing importance in an era of multiple treatments. To assess the presence of interaction, McAlister *et al.* suggested the use of 'interaction ratio' – a comparison of the effect of each treatment in the presence or absence of the other treatment. The interaction ratio is 1 in the presence of no interaction, above 1 in the presence of synergy and below 1 when there is antagonism.

Factorial trials are usually done for reasons of efficiency, because their design is also statistically more powerful. Together with the standard analysis 'inside the table', the main analysis in factorial trials compares the outcomes in all patients who received treatment A (with or without treatment B) with the outcomes of all patients receiving treatment B (with or without treatment A). As reported in Table 1, the efficacy of treatment A can be determined by comparing outcomes among all patients treated with A (i.e., cell AB and A0) with those of all patients not treated with A (i.e., cells B0 and 00) (see Table 1). Similarly, the efficacy of B is assessed by comparing cells AB and B0 with cells A0 and 00. These results may be seen as relating to the margins of the 2 × 2 table and this is why this kind of analysis is called 'at the margins'.

A factorial design allows investigators to obtain evidence about efficacy from fewer patients that would be needed if A and B were individually tested in two separate trials: by separately randomizing to two treatments it is possible to do two (or more) trials for little more than one alone (McAlister *et al.* 2003). However, it is worth noting that combining two treatments in the same arm does not necessarily mean that an RCT is a factorial trial. For instance, if a trial is carried out specifically to investigate whether there is an interaction between two treatments, this study should compare each of two active treatments on its own with both combined, without a placebo group. Such a trial is not a factorial trial (Higgins & Green, 2011).

In the scientific literature, factorial trials are difficult to find because there is no MeSH term (MEDLINE Subject Heading) to identify them, so a great deal of manual searching is usually required. In terms of study quality, even if the main methodological issues to assess quality (randomization, allocation concealment, blinding, etc) are similar in all RCTs, the reporting of factorial trials has yet to be agreed and standardized. The CONSORT Statement was intended to improve the reporting of RCTs, enabling readers to understand trial's methodological features and to assess the validity of its results, however, the main CONSORT Statement is based on the standard 2-group parallel design (www.consort-statement.org). There are several different designs of randomized trials, but only cluster trials, non-inferiority and equivalence trials, and pragmatic trials are covered by a specific CONSORT Statement. The reporting of factorial trial is often variable (McAlister *et al.* 2003): both 'inside the table' and 'at the margins' data are required for the proper interpretation of factorial trials and this is not always the case (Table 1). International standards for full and accurate reporting of the conduct and analysis of factorial trials (such as the CONSORT statement) are urgently needed (Montgomery *et al.* 2011).

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Conflict of Interest

None.

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