ABC of Methodology

This is a Section of *Epidemiologia e Psichiatria Sociale*, that regularly covers methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

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

What is a run-in phase?

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Abstract. Run-in periods are frequently used when designing a clinical trial. In this paper we analysed the implications of run-in periods for interpreting the results of clinical trials and applying these results in clinical practice. Study reports should indicate in details how run-in periods were carried out.

KEY WORDS: run-in, randomized controlled trial, validity, statistics.

The main phases of a randomized controlled trial (RCT) have been described in previous issue of the Journal (Cipriani & Geddes, 2009). In this brief article we will focus on run-in phases. Not all trials have run-in phases but the decisions of the whether to adopt one, and how to use it are some of the most important issues when designing and conducting a clinical trial.

After screening of participants, the run-in phase is the period of time which is used to select or exclude patients in a clinical trial before randomization. Run-in periods might be used to exclude non-compliant subjects, placebo responders or subjects who could not tolerate or did not respond to active drug. For this reason run-in periods have implications for interpreting the results of clinical trials and applying these results in clinical practice. Run-in phases are usually single blind (only the study staff - and not the patient - is aware of the real nature of the medication) but may be also unblinded (also known as open label). Before entering run-in phase, written informed consent has to be signed by study participants. Run-in phases can use either placebo (or no-treatment) or active therapy depending on the investigator's objectives.

Placebo run-in phases are used to screen out placebo responders in situations when there is a known high rate of placebo response (for instance, the majority of short-term selective serotonin reuptake inhibitors versus placebo trials). In this situation they can be moderately effective at increasing the post-randomisation separation between placebo and active drug - although they cannot prevent artefactual causes of apparent high placebo response such as baseline inflation of score of the investigator (DeBrota *et al*., 1999; Quitkin *et al*., 1998).

Active run-in phases, on the other hand, can be used to restrict participation in a clinical trial to those patients who either respond to a treatment, or are adherent during the run-in. Restricting to compliant participants may be essential in situations when adherence known to be low (i.e. for primary prevention, or in bipolar disorder) because excessive post-randomisation drop-out can make a trial fail to produce useful of valid results. Active run-ins may thus increase the efficiency and power of the study (Accordini, 2007). Even though they may increase internal validity, run-ins may affect generalisability and

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the overall applicability of findings (Cipriani *et al*., 2009). The effect may be to increase or decrease applicability. An active run-in can quickly identify and exclude individuals who may be unable to tolerate the medication being tested in a long-term trial. This might enhance the clinical applicability of the results. For instance, long-term treatment of bipolar disorder (or schizophrenia) is supposed to be a treatment specifically intended to prevent recurrence of mood episodes. Subjects who are entering a long-term trial are asked to take the study medication (or the combined study medications) for a long period of time. In real-world clinical setting, people who are prescribed long-term treatments will usually be selected from those who have been able to tolerate the medication in the short-term. In these studies a run-in design (that is a run-in phase with active long-term treatments before randomisation) may maximise the study power through participants' better compliance. Individuals who lose interest early on (potential "drop-outs") can then be excluded before random allocation. Similarly, any subjects who feel they may have an indication to receive the intervention treatment (potential "drop-ins") can also withdraw before randomisation. This potentially lowers rates of anticipated non-compliance to allocated treatment during a trial, resulting in a smaller required sample size (once randomised, these participants would generally be included in an intention-to-treat analysis).

Run-in periods can also dilute the clinical applicability of the results of a RCT because, compared with results that would have been observed without the run-in period, the reported results might overestimate the benefits and underestimate the risks of treatment (Pablos-Méndez *et al*., 1998). Moreover, because the reported results might apply to subgroups of patients who cannot be defined readily based on demographic or clinical characteristics, the applicability of the results in clinical practice might be further diluted. The clinical interpretation of an RCT must take into account the effect of the run-in. For this reason reports of RCTs using run-in periods should indicate how this aspect of their design might affect the application of the results to clinical practice. The implications of run-in on applicability are not always fully considered. For example, the results of an RCT investigating the long-term effects on relapse prevention in which patients are selecting according to short-term response to the active agent only directly apply to patients who have responded to the active agent in the short-term, not all patients. Systematic reviews need to consider the aims and designs of any run-in phases and details should be included in the CONSORT flow-chart (www.consort-statement.org).

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