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 randomised controlled trial?

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As quantitative, comparative studies, randomized controlled trials (RCTs) are designed to determine whether an association exists between treatment and outcome, and in clinical research RCTs are recognised as the most rigorous way of assessing the efficacy of interventions. However, RCTs are generally more difficult, costly and time consuming than other study designs. The Consolidated Statement of Reporting Trials (CONSORT) provides readers of RCTs with a list of criteria useful to assess trial validity (for full details visit www.consort-statement.org).

The main phases of a RCT are shown in the Figure.

1. PRE-STUDY PHASE

Before starting to design a RCT, two key questions are to be asked:

- is the tested intervention well enough developed to permit evaluation?
- is there enough preliminary evidence that the intervention is likely to be beneficial?

When planning a RCT, it is now common for trialists to carry out a systematic review of the available evidence to answer these questions (this evidence may come from observational studies).

First, a study protocol has to be written. It should be as detailed as possible, describing every step of the study (e.g. identification of the problem, application of the results) and answering relevant questions (are the objectives consistent with the study question? does the study design achieve these objectives? which is the public health impact of the findings?). In the protocol, researchers need to report all information about the conduct and analysis of the trial (e.g. criteria for inclusion or exclusion of the study population, data handling, data analysis plan). In parallel with the protocol, it is necessary to prepare all other required trial documents such as subject information sheets and informed consent forms (for example, visit http://www.dh.gov.uk/en/Publichealth/Scientificdevelopmentgeneticsandbioethics/Consent/Consentgeneralinformation/DH_4015950).

As experimental studies that modify routine clinical practice, RCTs have to be approved by the local Ethics Committee. All study participants have to be informed about study characteristics and provide written informed consent before enrolment into the trial. The protocol should also be registered for publication in dedicated websites. Based on both ethical and scientific reasons, since 2000 web-based registers (such as ClinicalTrials.gov and Controlled Clinical trials) have been recording trial protocol information. This progress in the public registration of clinical trials worldwide is important because it allows clin-

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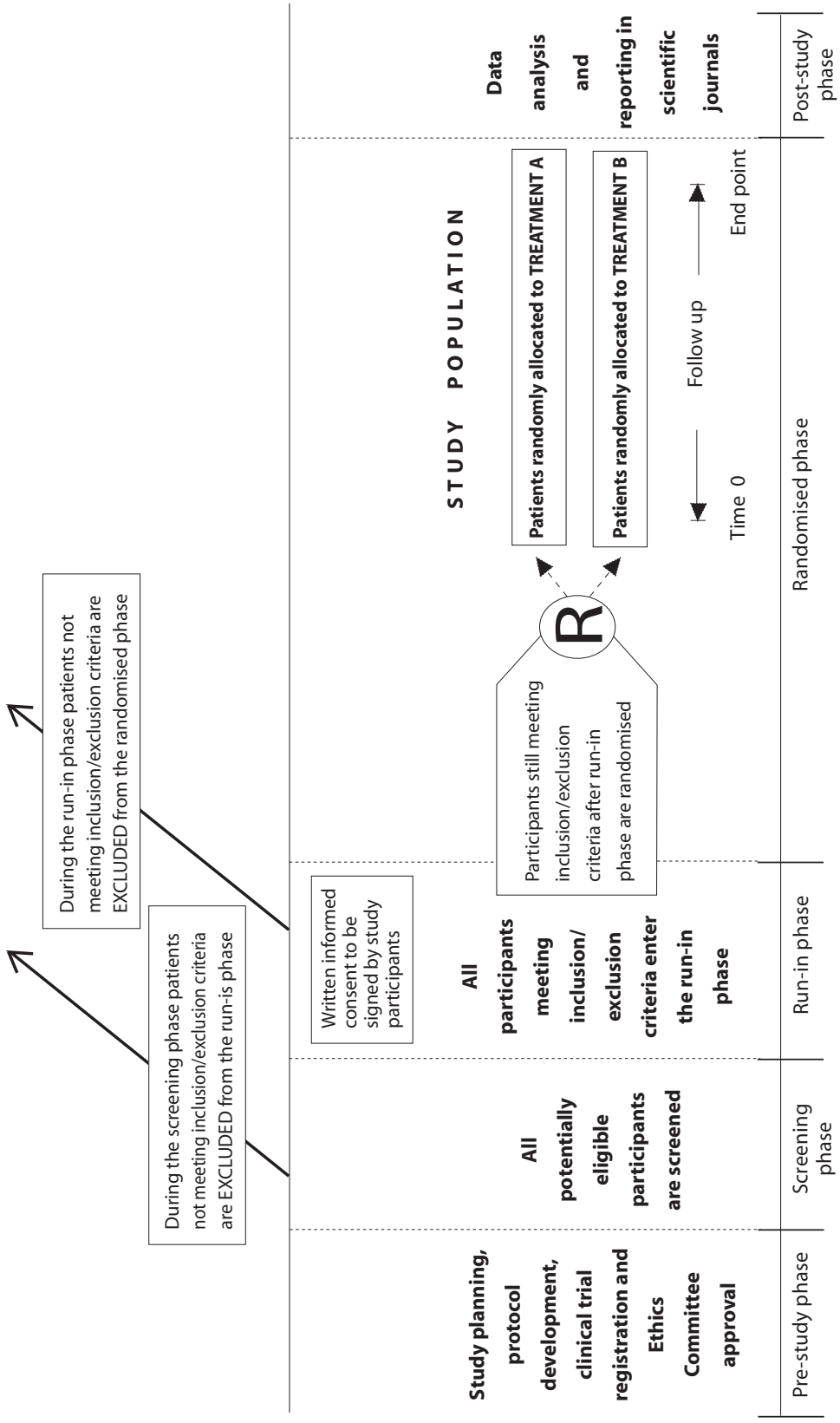


Figure 1

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icians and researchers to see in advance details about study conduct and analysis in a more transparent way.

2. SCREENING PHASE

Information gathered during the screening phase is used to document their baseline clinical conditions and to make decisions on participants' study eligibility. Therefore, the threshold for access to assessment should be set at a low enough level to ensure people are not screened out before full information on their needs is obtained.

3. RUN-IN PHASE

Run-in phases are pre-randomization periods being used to select or exclude patients in a clinical trial, after eligibility criteria are met (Pablos-Méndez *et al*., 1998). 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 (we will discuss the arguments of this paragraph in the next issue of the journal).

4. RANDOMISED PHASE

Randomisation

The main reason for using randomisation to allocate treatments in a controlled study is to try to prevent biases (Schulz *et al*., 1995). Randomization is a process that aims at producing groups that are similar in terms of clinical, demographic and prognostic factors. Random allocation ensures that there are no systematic differences between intervention groups in factors, both known and unknown, that may affect outcome. Random allocation ensures that each patient has a known, equal chance of being given each treatment, and that the treatment that will be allocated cannot be predicted.

Allocation concealment

Allocation concealment refers to the process used to ensure that subjects, investigators and all other health care providers involved in the conduct of the study are unaware to which group participants will be allocated to prior to random allocation. Allocation concealment is essential to prevent patients being selected for the trial in the knowledge of which treatment they will receive.

Blinding

Blinding refers to the process whereby people are kept unaware of which treatment an individual patient has been receiving. Blinding (or "masking") differs from allocation concealment in that it also applies post-randomisation (Cipriani *et al*., 2008).

Choice of interventions and outcomes

A key component of a RCT is to specify the interventions of interest and the interventions against which these will be compared (the so-called *comparisons*). One of these treatments is a treatment commonly used in clinical practice (*standard* or *control* treatment); the new treatment to be tested in the study is named *experimental* (or *investigational*) treatment. The control might be an inactive control intervention (such as placebo, no treatment, standard care, or a waiting list control), or an active control intervention. When specifying drug interventions, factors such as the drug preparation, the route of administration, the dose, duration and frequency of administration should be considered and clearly specified in the study protocol because they might influence the outcome estimate and the external validity of the study (Cipriani *et al*., 2009).

RCTs should also clearly identify a primary outcome (on which to base the calculation of sample size and, hence, trial design) and include all outcomes that are likely to be meaningful to patients and clinicians. Outcomes may be measured objectively (number of relapse, number of hospitalisations) or subjectively as rated by a clinician, patient, or carer (for instance, severity of illness scales or disability scales). In other fields of medicine it is common to use *hard outcomes*, (that is, objective outcomes like mortality rates, concomitant medications, return to work). By contrast, in psychiatric trials changes in rating scale scores are more commonly reported which are inherently more susceptible to bias.

5. POST-STUDY PHASE

There are various kinds of analysis of data from RCT. One way is to include data only on participants whose results are recorded, using as a denominator the total num-

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ber of people who had data recorded for the particular outcome in question. Another way is to use the total number of randomized participants, irrespective of whether some participants withdrew the study (Intention to treat analysis – ITT analysis). ITT analysis maintains the advantages of random allocation, which may be lost if subjects are excluded from analysis through, for example, withdrawal or failure to comply. ITT analysis is both more likely to avoid bias and to produce clinically meaningful results.

When data are analysed, results of RCTs are disseminated and published in scientific journals. To be published, study reports must undergo a peer-review process. Almost all the most important scientific journals want to see the study protocol before accepting a study for publication, in order to check the consistency between the protocol and the full report of the RCT.

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