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.

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What is a clinical trial protocol?

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Abstract. Trial protocols are documents that describe the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials. Trial protocols provide the background and rationale for conducting a study, highlighting specific research questions that are addressed, and taking into consideration ethical issues. Trial protocols must meet a standard that adheres to the principles of Good Clinical Practice, and are used to obtain ethics approval by local Ethics Committees or Institutional Review Boards.

KEY WORDS: study protocol, outcome, randomized controlled trial, rating scale, statistics.

Trial protocols are documents that describe the objectives, design, methodology, statistical considerations and aspects related to the organization of clinical trials. Trial protocols provide the background logic and rationale for conducting a study, highlighting specific research questions that are addressed, and taking into consideration ethical issues. Before starting a randomized controlled trials (RCT), two key questions have to be answered:

- is the tested intervention sufficiently well developed to permit evaluation?
- is there enough preliminary evidence that the intervention is likely to be beneficial? (it should be borne in mind that most frequently this evidence comes from observational studies).

The protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications and dosages, the length of the study (i.e. follow up) and the primary outcome. The latter point is of crucial importance to avoid "data dredging". Data dredging (also called as *data fishing* or *data snooping*) is the inappropriate use of data mining to uncover misleading relationships in data. These relationships may be valid within the test set, but they are likely to be by chance alone so they have no statistical significance in the general population. Secondary outcomes can also be taken into account when designing a clinical study. Secondary outcomes are used to explore possible associations between clinical variables but they have to be only a few and a priori defined to reduce the risk of multiple comparisons (Esposito *et al*., 2009). Researchers should be aware that conducting an clinical trial without a hypothesis can lead to premature (and possibly wrong) conclusions.

The existence of a protocol for RCTs allows researchers at multiple locations (for instance, in a multicenter trial) to perform the study in exactly the same way, so that their data can be combined. The protocol also gives the coordinating centre as well as the local researchers a common reference document for the researchers' duties and responsibilities during the trial. Some journals, such as *Trials*, aim at specifically publishing trial protocols (Nose *et al*., 2009).

The development of a new pharmaceutical agent is conventionally divided into several phases, with the initial pre-

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clinical toxicity and pharmacological work leading to small preliminary trials in human volunteers (phase I), then small (perhaps 30-50 participants), usually randomized, studies in patients, before the pivotal phase III RCTs of efficacy and safety. Noncommercial trials will try to replicate this approach. The retrieval of preliminary data will need to inform the estimation of the size of the likely treatment effect, dose, and safety. Such information is needed to estimate the sample size of the study and to justify the expenses of a larger trial. When planning an RCT, it is now common for trialists to carry out a systematic review of the available evidence to answer these questions (Tyrer, 2008).

The trial protocol should be as detailed as possible, describing every step of the study (e.g., identification of the problem, application of the results, etc.) and answering relevant questions (Are the objectives consistent with the study question? Does the study design achieve these objectives? What 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 the inclusion or exclusion of the study population, data handling, and data analysis plan). The lead author of the protocol needs to identify individuals with relevant experience to contribute to the protocol and to provide statistical input or technical information. All protocols must meet a standard that adheres to the principles of Good Clinical Practice, prior to being submitted to the Ethics Committee or Institutional Review Board (for details, see the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – ICH, available at http://www.ich.org/cache/compo/276-254-1.html). After preparation, the first draft of the protocol should be peer reviewed, ensuring that all points have been incorporated or discussed further within the review team. In parallel with finalizing the protocol, it is necessary to prepare all other necessary trial documents, such as subject information sheets and informed consent forms (an example can be found on the Web at the following address: http://www.dh.gov.uk/en/index.htm).

Once the protocol and other relevant documentation are ready, applications should be made to the Ethics Committee. As for experimental studies that have the potential of risk to human subjects, all related RCTs have to be approved by an Ethics Committee before patient recruitment is started. All study participants must be informed about the study characteristics; they must provide written informed consent before enrollment into the trial. In some circumstances, an RCT may be ethical but difficult to carry out (or even unfeasible). One reason might be difficulties with randomization or recruitment (Fairhurst & Dowrick, 1996). For example, once an intervention becomes widespread, it can prove impossible to recruit clinicians who are willing to "experiment" with alternatives. This might be true for some widespread practices in clinical psychiatry that are actually not backed by randomized evidence. For example, it is not clear whether anticholinergic drugs work better than levodopa against extrapyramidal side effects in patients with schizophrenia who take long-term antipsychotic medications; however, in daily clinical practice clinicians are reluctant to use specific antiparkinsonian drugs (such as levodopa) that might trigger psychotic symptoms. Strong patient preferences may also limit recruitment and bias outcomes if not accommodated within the study design (Brewin & Bradley, 1989).

The protocol should also be registered for publication in dedicated Web sites. Based on both ethical and scientific reasons, since 2000 major registries (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 clinicians and researchers to see in advance details about study conduct and analysis in a more transparent way. The number of registered trials increased dramatically in 2005 after the requirement for registration was introduced by several medical journals, led by the International Committee of Medical Journal Editors.

REFERENCES

Brewin C.R. & Bradley C. (1989). Patient preferences and randomised clinical trials. *British Medical Journal* 299, 313-315.

Cipriani A. & Geddes J.R.. (2009). What is a randomised controlled trial? *Epidemiologia e Psichiatria Sociale* 18, 191-194.

Esposito E., Cipriani A. & Barbui C. (2009). Outcome reporting bias in clinical trials. *Epidemiologia e Psichiatria Sociale* 18, 17-18.

Fairhurst K. & Dowrick C. (1996). Problems with recruitment in a randomised controlled trial of counselling in general practice: causes and implications. *Journal of Health and Service Research Policy* 1, 77-80.

Nosè M., Accordini S., Artioli P., Barale F., Barbui C, Beneduce R., Berardi D., Bertolazzi G., Biancosino B., Bisogno A., Bivi R., Bogetto F., Boso M., Bozzani A., Bucolo P., Casale M., Cascone L., Ciammella L., Cicolini A., Cipresso G., Cipriani A., Colombo P., Dal Santo B., De Francesco M., Di Lorenzo G., Di Munzio W., Ducci G., Erlicher A., Esposito E., Ferrannini L., Ferrato F., Ferro A., Fragomeno N., Parise V.F., Frova M., Gardellin F., Garzotto N., Giambartolomei A., Giupponi G., Grassi L., Grazian N., Grecu L., Guerrini G., Laddomada F., Lazzarin E., Lintas C., Malchiodi F., Malvini L., Marchiaro L., Marsilio A., Mauri M.C., Mautone A., Menchetti M., Migliorini G., Mollica M., Moretti D., Mulè S., Nicholaou S., Nosè F., Occhionero G., Pacilli A.M., Pecchioli S., Percudani M., Piantato E., Piazza C., Pontarollo F., Pycha R., Quartesan R., Rillosi L., Risso F., Rizzo R., Rocca P., Roma S., Rossattini M., Rossi G., Rossi G., Sala A., Santilli C., Saraò G., Sarnicola A., Sartore F., Scarone S., Sciarma T., Siracusano A., Strizzolo S., Tansella M., Targa G., Tasser A., Tomasi R., Travaglini R., Veronese A., Ziero S. (2009). Rationale and design of an independent randomised controlled trial evaluating the effectiveness of aripiprazole or haloperidol in combination with clozapine for treatment-resistant schizophrenia. *Trials* 10, 31.

Tyrer P. (2008). So careless of the single trial. *Evidence Based Mental Health* 11, 65-66.