What We Talk about When We Talk about Randomized Controlled Trials

Alfredo Chetta Dario Olivieri

Respiratory Disease and Lung Function Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy

When we talk about randomized controlled trials (RCTs), we talk about rigorous interventional experiments that have been developed to control for possible biases that can be present in observational studies [1]. RCTs restrict the possible systematic errors by means of a well-defined and controlled setting, blinding, allocation concealment, randomization, strict inclusion and exclusion criteria and so on, thereby reaching a high internal validity, i.e. the ability to determine a cause-effect relationship. For this reason, RCTs fall into the trial category with an 'explanatory' approach according to the definition of Schwartz and Lellouch [2]. Well-designed RCTs carried out in large samples of a population provide international guidelines with the strongest category of evidence-based medicine.

However, the same features that ensure the internal validity of RCTs can, on the other hand, severely limit their external validity, i.e. the ability to generalize the results in a clinical setting and in the general population. Notably, the strict inclusion and exclusion criteria followed by RCTs in the recruitment of the patients represent the chief limitation to generalizing their results. An advanced age, too-mild or too-severe airflow obstruction, no smoking habit, no long-term oxygen therapy, no other lung diseases and no comorbidities are the selection

criteria usually adopted by the main RCTs on COPD treatment. It really is questionable whether the results from RCTs based on such selection criteria can indeed be extended to a larger 'real-life' population of patients with COPD. Herland et al. [3] studied a large population of patients with obstructive lung disease who were classified as having asthma (38%), COPD (42%) or were included in a mixed group (20%). In this study, absence of comorbidity, a FEV₁ 50–85% of predicted value, present or historical reversibility, being either a nonsmoker or an exsmoker with a smoke burden <10 pack-years were considered as selection criteria of asthmatic patients to a RCT. The authors found that only 5.4% of their asthmatic patients met these criteria. They applied the same procedure to the group of COPD patients and a FEV₁ <70% of predicted value, a significant smoking history (>15 pack-years) and absence of atopy were the selection criteria they considered. Only 17% of the COPD patients were eligible for the RCT. In line with these results, Travers et al. [4] found that in a group of 55 COPD patients undergoing treatment and identified by postal questionnaire and functional assessment, only a negligible percentage met the eligibility criteria of 18 RCTs cited in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

The paper by Scichilone et al. [5], published in this issue of *Respiration*, confirms and further extends the results of the studies by Herland et al. [3] and Travers et al. [4]; the authors found that 83% of 696 consecutive outpatients with COPD lacked at least one of the eligibility criteria for a RCT. Pulmonary disease other than COPD, long-term oxygen therapy, lung function, age and extra-pulmonary comorbidities were, in descending order, the most frequent causes for exclusion from RCTs. Interestingly, of 118 patients with COPD deemed eligible for RCTs, none belonged to GOLD stage 1. Compared to the studies by Herland et al. [3] and Travers et al. [4], the study by Scichilone et al. [5] included a larger number of patients with a clinically and functionally established diagnosis of COPD.

When we talk about RCTs on which the GOLD treatment guidelines are based, we talk about RCTs which may largely show a limited external validity. This point is not at all trivial because RCTs absorb large economic resources and the increased costs of healthcare in resource-limited conditions require more and more evidence of being effective and applicable in the clinical setting.

According to Schwartz and Lellouch [2], a clinical trial can show either an ‘explanatory’ approach or a ‘prag-

matic’ approach. The explanatory approach is aimed at understanding while the pragmatic approach is aimed at decision [2]. In other words, unlike the explanatory trials, the pragmatic trials are designed to show the effectiveness of an intervention in real life, rather than its efficacy merely in well-defined and controlled settings [6]. To maximize external validity, the pragmatic trials consist of simple designs applied in different clinical settings, measure a wide spectrum of outcomes (mostly patient-centered) and require large sample sizes to overcome the heterogeneity of the setting [6]. Pragmatic trials are mostly phase IV studies [6]. It is of note that policy-makers are increasingly interested in pragmatic trials because these seem to be able to provide valid and reliable information about what works best in healthcare [7].

As is the case with explanatory trials, pragmatic trials are also not free of limitations, the most important of which pertains to the same concept of ‘real life’ when it is translated into a research setting. What emerges as applicable in Europe from a pragmatic trial carried out in Europe is not necessarily applicable in another part of the world. Therefore, explanatory trials, in general, and RCTs, in particular, should not be replaced by pragmatic trials, but should rather be complemented with them.

References

- 1 Grimes DA, Schulz KF: Bias and causal associations in observational research. *Lancet* 2002;359:248–252.
- 2 Schwartz D, Lellouch J: Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis* 1967;20:637–648.
- 3 Herland K, Akselsen J-P, Skjøsberg OH, et al: How representative are clinical study patients with asthma or COPD for a larger ‘real life’ population of patients with obstructive lung disease? *Respir Med* 2005;99:11–19.
- 4 Travers J, Marsh S, Caldwell B, et al: External validity of randomized controlled trials in COPD. *Respir Med* 2007;101:1313–1320.
- 5 Scichilone N, Basile M, Battaglia S, et al: What proportion of COPD outpatients is eligible for inclusion in randomized clinical trials? *Respiration* 2014;87:11–17.
- 6 Patsopoulos NA: A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci* 2011;13: 217–224.
- 7 Tunis SR, Stryer DB, Clancy CM: Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* 2003;290:1624–1632.