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Enrolling Patients Into Multiple Trials: It Is Time for Glasnost*

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In this issue of *Critical Care Medicine*, Cook et al (1) reported on the results of an observational study that investigated the prevalence and characteristics of coenrollment (defined as patients' simultaneous or sequential enrollment in two or more trials) (2) in the OSCILLation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial, an international multicenter randomized clinical trial (RCT) comparing high-frequency oscillation with conventional ventilation in patients with acute respiratory distress syndrome (3), conducted at 39 ICUs in five countries over a period of 4 years and founded by the Canadian Institute for Health Research. Of 548 patients randomized in that work, 127 patients (23.2%) were coenrolled in other studies (25 additional studies; median, 1.1; range, 1–4) by 17 ICUs. Overall, the proportion of patients coenrolled did not differ between the treatment and control arms of the OSCILLATE trial, and there were no differences in demographic data or severity of illness between patients coenrolled and not coenrolled and in the characteristics of participating centers and research personnel who did enroll patients in multiple trial versus those who did not, unless that research coordinators with more experience showed a higher tendency to coenrollment. Predictors of coenrollment in a multivariate analysis included patients' age, with younger patients more likely to be coenrolled, investigators' and research coordinators' experience, ICUs with more than 26 beds, and centers located in Canada. Side and adverse event proportion did not change when adjusting for patients coenrolled in other studies, nor coenrollment did modify the treatment effect. These results are not surprising and confirm similar findings of these (4–6) and other researchers (7–9); however, an interesting point of Cook et al (1) was to have nested prospectively the study on coenrollment into the main study OSCILLATE, so as to gather data that are often nonreported or difficult to obtain post hoc. Coenrollment was more likely in Canada than in other countries; however, 74.8% patients were from Canadian ICUs, and 69.3% of additional studies were affiliated to Canadian Critical Care Trial Group, and this, as clearly stated by authors, can be a hindrance to data generalization. On the other side, the affiliation to collaborative research networks positively impact on multicenter trials participation (3, 5, 6, 10, 11), thus increasing the chances to be involved in multiple studies, since the choice of collaboration partners is significantly affected by previous working relationships and other members' reputation.

Major reported concerns on coenrollment are about patients' safety (2, 4, 6–8, 11, 12), consent liability (8, 11, 13, 14), physicians and staff unwillingness (4, 8, 11, 12), and scientific integrity (15, 16). Available literatures agree that coenrollment does not influence patients' safety, trials outcomes, or adverse and side effects, as also confirmed in article by Cook et al (1), provided that eligibility criteria of every study are correctly applied and that single-study treatments are not sub- or superadditive (7, 9). About informed consent, it could be a significant barrier to enrollment, mostly in patients without decision-making capacity as usually ICU patients are: recent data on coenrollment in ICUs, however, showed that reasons for accepting coenrollment, both in children and adults, are more related to a clear comprehension of study aims and treatments or concerns about safety than to study number (7, 8, 14). Empathy between staff and patients or relatives is also a factor that increases the consent. Cook et al (1) reported that investigators' experience was a predictor of coenrollment: this confirm that consent procurement is a skill that can be learned and the central importance of the "human factor" in conditioning attitudes toward research (2, 4, 14), even in teaching hospitals that usually carry on more than one RCT at the same time and are, or should be, better equipped and with more motivated staff, as were 38 of 39 participating to OSCILLATE. Regrettably, Cook et al (1) do not report data on

*See also p. 328.

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consent refusal; it is therefore difficult to infer if 421 patients were not coenrolled because not meeting eligibility criteria for the secondary study, because of lack of consent or for environment barriers. A further striking data reported in this issue of *Critical Care Medicine* is that of 574 patients eligible but not randomized into the OSCILLATE, only 24 patients (4.2%) were not coenrolled because they were previously included in studies not permitting coenrollment. The remaining 530 were not further analyzed, but this underlines the need for implementing strategies to increase recruitment into research trials (17, 18). Contextual circumstances in participating centers may influence noninvestigator practitioners' readiness for collaboration or create barriers for research personnel in accessing potential participants, as well as the need to obtain consent for more than one trial can be perceived as an adjunctive workload: increasing staff's awareness of the studies and addressing potential conflicts before starting to recruit can be a facilitator clue (4, 11, 12). About scientific integrity, taking for granted that a collaboration between researchers and industry is necessary for advancing scientific knowledge, accountability of industry-founded trials is perceived by the public and professionals as a major issue, that needs to be addressed by promoting transparency all along the trial process (15, 16, 18, 19). Actually patients recruitment can be biased by industry policies that "tout-court" prohibit coenrollment and force physicians to choose amid "competing" trials. It is interesting to note that Cook et al (1) report that only 16 of 127 patients (12.6%) were coenrolled in industry-founded trial.

The quality of every step in the research practice is of the utmost importance for the scientific and general communities, since evidence-based results are used from the macrolevel of policy makers and stakeholders until the microlevel of individual clinical decisions; their applicability to different health systems is thus an essential requisite. On the other side, the need for evidence-based data to assess new treatments and interventions increases the demand for RCTs and for large sample sizes (10, 12, 18, 19). Therefore, enrolling a sufficient number of participants in a reasonable lapse of time becomes a major challenge for researchers and founding bodies (17, 19–22). Under these conditions, patients' enrollment in multiple trial was proposed as one potential way to accrue cases recruitment (2, 6, 10, 13, 21, 22). However, in the absence of clear-cut international guidelines, coenrollment remains often a choice of the investigator on its own, seldom regulated by local research ethics boards, whose policies on the matter are rarely available and highly variable from site to site (2, 4), as confirmed in this issue of *Critical Care Medicine*. Furthermore, coenrollment is rarely reported, making the appraisal of the real impact of this practice very difficult (9, 18, 19).

In conclusion, the development and validation of international guidelines is needed to support patients, clinicians, and ethics committees in assuming decisions about coenrollment. In the meanwhile, the scientific community is called to strongly claim for transparency in data reporting.

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