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EDITORIAL

Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? No

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Randomized controlled trials (RCTs) with appropriate question selection, careful subject enrollment, adequate powering and assiduous execution of a well-designed protocol can provide convincing data that improve the strength of the evidence base guiding practice. However, many RCTs conducted in intensive care medicine have resulted in no significant differences in primary outcomes between the tested groups. This is particularly true for trials targeting mortality. Because patients in RCTs in critical care medicine—and patients in intensive care units (ICUs)—have wide variability in their risk of death, these patients will also have wide variability in the absolute benefit that they can derive from a given therapy. If the adverse effects of the therapy are not perfectly aligned with the treatment benefits, this will result in heterogeneity of the treatment effect, wherein different patients experience quite different and often unexpected results from therapy. As a consequence, in a negative RCT, there are patients who experience benefit and others who experience harm, all merged into the global result. Therefore, the results do not provide a definitive answer to the study question or enable reliable guidance or recommendations to be developed. Indeed, these negative clinical trials seldom convey useful information beyond that stemming from an examination of their subgroups, their possibly inopportune assumptions and their deficiencies of design.

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For a contrasting viewpoint, please go to https://doi.org/10.1007/s00134-018-5129-5

Why are so many RCTs in critically ill patients negative? First, most studies use all-cause mortality as the targeted outcome, but the underlying cause of death, perhaps especially in ICU patients, is highly variable and can be influenced by multiple elements, including comorbidities, treatment choices, personal preferences and other unaccounted factors that can blur the effects of the intervention. Moreover, the intervention may be effective but not influence the overall mortality of the group. Surrogate or intermediate endpoints that are better indicators of potential effect help to improve sensitivity. This has been shown to be true in studies on the management of acute respiratory failure [1] and optimal nutritional support.

Second, we should remember that the comparison between groups of an RCT tests whether any observed difference cannot be explained statistically by chance alone (rejects the null hypothesis). To achieve this purpose, the patient population must be carefully selected, and there must be a clear rationale for a difference to be expected—an element that is often missed during trial design. The risk of type II error in RCTs is not the only issue. Indeed, in most negative trials, there was not even a suggestion of a positive outcome. Ability to indicate a difference between groups is more a matter of disease severity, especially when a reduction in mortality is the target [2]. These issues are well illustrated by two recent trials on the use of corticosteroids in septic shock. One (the ADRENAL study) reported no difference in mortality when the placebo group mortality rate was 29% [3], but the other (the APROCCHSS study) showed a significant difference when the placebo group mortality rate was 49% [4]. The ADRENAL trial [3] enrolled patients at a rate approximately five times higher than other large trials in septic shock, but only about half the patients

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Box 1 Some perceived benefits that motivate clinicians to participate in large multicenter randomized controlled trials (RCTs)

Scientific (to address an important question)
Practical/pragmatic (benefit for patient care)
Financial (benefit for the department)
Political (benefit for the hospital/group)
Academic (for individual recognition/promotion)
Societal (benefit for society)

were receiving significant doses of norepinephrine, and the mortality rate was less than 30%. Too many trials, under pressure to enroll a large number of patients over a short time period (Box 1), capture patients who meet the inclusion criteria but do not really represent the population most likely to benefit from the study intervention. The negative results of a large RCT testing a precise question with clear and rational alternatives, appropriate patient selection, and thoughtful design and execution have clear potential to yield more informative results. Unfortunately, such criteria are seldom met in critical care.

Third, conditions such as sepsis or ARDS are not diseases but syndromes, originating from a variety of causes and mechanisms. The rapidly advancing field of biomarker identification may eventually help in patient identification and selection, but we are not there yet. To improve outcomes in complex critically ill patients with these syndromes, the underlying causative disease must be taken into consideration. As an example, randomization of patients with septic shock to a lower versus higher blood pressure target will almost certainly yield negative results [5], because some patients, e.g., those with atherosclerosis and arterial hypertension, may require a higher arterial blood pressure than their younger counterparts with fewer comorbidities. These negative results could be incorrectly interpreted as meaning that the blood pressure level is not important in septic shock and that all patients can be left with a mean arterial pressure of 65 mmHg; clearly this is not appropriate.

It is important not to overinterpret the results of negative RCTs. After all, lack of proof of benefit does not imply proof of lack of benefit. Incorrect interpretation of a negative trial may have serious consequences for patient care and for the advancement of our field. This is also illustrated by RCTs supporting restrictive strategies on blood transfusion in critically ill patients. The randomization of patients according to hemoglobin thresholds in those influential studies should be viewed as suboptimal, as it is clear that the decision to transfuse should not be based only on this information, but on other factors, including underlying coronary disease [6]. In these studies on transfusion, enrollment rates were quite low, largely because physicians preferred to transfuse some patients who may have been study candidates but for whom they considered ethical or scientific equipoise was not present. Hence, these enrolled patients may actually not have needed a blood transfusion and were unlikely to benefit. Similarly, the negative trials on early goal-directed therapy in patients with sepsis could have been anticipated, with many patients requiring no aggressive intervention because they were either already resuscitated or only mildly ill [7]. With the lack of evidence of an impact on patient outcome, some clinicians became skeptical about the need for central venous catheters and some have moved away from cardiac output assessment.

Because negative trials carry serious and often unintended consequences, there is a pressing need to address the major problems in design and execution before undertaking them. For example, authorities and decision-makers may use the results of negative trials to justify avoiding the costs of sporadically useful but unproven interventions. This is why the need to conduct RCTs for extracorporeal membrane oxygenation (ECMO) has generated so much controversy [8]; a negative clinical trial may hinder reimbursement of this potentially lifesaving procedure. From the viewpoint of industry, negative RCTs decrease enthusiasm to develop new medications for sepsis, and the idea that critical care is a very difficult area in which to perform clinical trials is becoming increasingly established, limiting investment in this field of research.

In summary, a negative RCT in a heterogeneous, poorly defined population provides little if any new information. It does not even tell us much about mechanisms. Separating heterogeneous patient populations into only two groups for the purposes of an RCT is a rather simplistic approach. For individual patients, optimal dosing is crucial to effectiveness: applying a single PEEP level [9], the same amount of fluid, the same blood pressure value, the same transfusion trigger in all patients makes no sense. The main message of a negative trial in critically ill patients is that the decision process is more complex than one may think and treatment should be targeted to the needs of the individual, rather than to heterogeneous groups of patients. In a sense, it is reassuring that negative RCTs stress the complexity of critical care medicine and the need for careful reflection at the bedside. The nosography of critical illness is still in its infancy, and we need to include appropriate biomarkers in our evaluations. We need to choose therapies according to the specific needs of individual patients and not offer the same treatments for all.

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Compliance with ethical standards

Conflicts of interest
JLV and JJM have no relevant conflicts to declare, AP has received research grants from Maquet and Drager, received travel grants from Getinge and consulted for Maquet, Xenios and Baxter. AP holds patents on CO_2 removal and other technologies of interest for ICUs.

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