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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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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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EDITORIAL

Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? Yes

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Introduction

Over the last half-century, the emergence and evolution of critical care has made possible the conduct of incredibly complex lifesaving surgery and the recovery of untold thousands of critically ill medical patients who previously had no chance of survival [1]. Despite this success, most interventions delivered to critically ill patients were adopted based on physiological theory or "borrowed" from other settings, e.g., positive pressure ventilation from the operating room and fluid resuscitation from the infirmaries and battlefields of the world wars. While this approach was entirely appropriate in the early days of our specialty, it is now clear that many standard practices of the past, and some new ones, harmed the very patients they were designed to help. We know this predominantly because academic researchers have designed and conducted high-quality, robust, pragmatic randomised clinical trials (RCTs); many of the trials that have improved the care of our patients have reported neutral or negative treatment effects.

Clinical trials in critical care

The conduct of RCTs in critical care is challenging; patients are rarely able to give or withhold consent, diagnosis may be unclear early in the clinical course, making complex inclusion criteria difficult to apply, interventions are often time-critical, and the natural trajectory of critical illness is incredibly variable. Although clinical trial methodology is continually evolving with exciting new methods such as adaptive and platform trials being brought to bear [2, 3], most high-quality evidence comes from traditional individual or cluster RCTs, which, simplistically, can be divided into efficacy and effectiveness trials [4]. Efficacy trials are designed to answer the question, "Does this intervention work in the ideal patient population in the ideal circumstances?" Efficacy trials typically use complex inclusion and exclusion criteria and are the appropriate design when investigating the likely impact of a new intervention [4]. Efficacy trials sacrifice the ability to apply their results to real-world practice in pursuit of maximal internal validity. In contrast, effectiveness trials, also called pragmatic trials, are designed to determine the effect of an intervention when it is used in more a diverse population or typical clinical settings [5]. Notable features include simplified inclusion and exclusion criteria that seek to maximise generalisability and thus to understand the true impact of new and established treatments on outcomes important to patients [5].

The impact of trials that demonstrate harm

On this background it is both rational and essential to test as many of the interventions used in critical care as possible. Priority should be given to interventions that are used for to many patients, interventions that are costly or labour intensive and those for which there is insufficient evidence to reliably estimate the balance between benefit and harm. That the risk of us causing harm to our patients is real is confirmed by a recent systematic review that reported on RCTs in critical care in which the intervention studied significantly affected mortality; mortality was increased by half the interventions studied

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Table 1 Randomised clinical trials done in the critical care setting where neutral results allowed changing clinical practice guidelines and/or clinical practice

Trial	Result	Practice change/benefit
TRICC [11]	In general ICU patients with anaemia, the use of a lower vs. higher Hb-threshold for transfusion did not affect 30-day mortality	Reduced blood transfusion in ICU patients reduces stress on transfusion services
Low-dose dopamine [12]	In ICU patients with SIRS and early renal dysfunction, the use of dopamine vs. placebo did not affect renal dysfunction	Use of dopamine may be stopped in general ICU patients if not beneficial as later studies showed use of dopamine was associated with increased adverse effects
SAFE [13]	In general ICU patients, the use of albumin vs. saline did not affect mortality or any other outcomes	The use of albumin may be stopped in general ICU patients, saving scarce resources
RENAL [14]	In ICU patients with AKI, higher vs. lower intensity CRRT did not reduce mortality at 90 days	The use of higher intensity CRRT may be stopped in ICU patients—significant economic benefits
PROWESS SHOCK [15]	In ICU patients with persistent septic shock, the use of APC vs. placebo did not affect mortality or any other outcome	APC removed from market, reducing risk of haemorrhagic complication and saving money
TRISS [16]	In ICU patients with septic shock and anaemia, the use of a lower vs. higher Hb threshold for transfusion did not affect mortality or any other outcome	Less blood may be used in patients with septic shock reducing stress on transfusion services
ABLE [17] TRANSFUSE [18]	In ICU patients with anaemia, fresher vs. standard issued or older blood did not affect mortality	The use of fresher blood may be stopped in ICU patients, reducing stress on transfusion services
PRISM [19]	In patients with septic shock in the emergency department, early goal-directed therapy vs. usual care did not affect mortality or any other outcome	Early goal-directed therapy may be stopped in patients with septic shock—economic benefits and avoidance of potentially harmful protocolised interventions
TTM [20]	In unconscious adult survivors of out-of-hospital cardiac arrest targeted temperature management at 33 °C versus 36 °C did not improve mortality or neurological recovery	Cooling to 33 °C is unnecessary meaning less intense therapy, use of less sedation and making earlier neurological prognostication possible

AKI acute kidney injury, *CRRT* continuous renal replacement therapy, *Hb* haemoglobin, *SIRS* systemic inflammatory response syndrome

[6]. Notably critical trials that report harm are generally of higher quality, being more likely to be multi-centred and blinded and have larger sample sizes [7]. Importantly, many interventions shown to be harmful in high-quality trials were in regular clinical use at the time of testing, including high-frequency oscillatory ventilation [8], hydroxyethyl starch [9] and intensive glucose control [10]. In reaction to these results, clinicians, guideline writers and regulators have taken actions to reduce the use of harmful interventions and thus to improve outcomes for our patients.

The impact of trials that report a neutral treatment effect

A positive, a neutral and a negative result for a given test of intervention X vs. intervention Y will be highly informative for clinicians, those writing clinical practice guidelines and policy-makers and healthcare funders provided the research is of high quality and free from significant risk of bias. The results of robust pragmatic trials allow everyone to change clinical practice with confidence. Some of the many RCTs with neutral results that have allowed us to provide better and more cost-effective care are listed in Table 1.

Simplifying critical care

Trials reporting neutral or negative treatment effects are important in the process of simplifying critical care as they show us what not to do. As many standard critical care interventions and therapeutic targets are being challenged, simplifying care becomes increasingly rational from the patient, organisational and financial perspective. Doing less may improve patients' outcomes, reduce the number of drug interactions and adverse events and save money. Doing less allows us to focus our efforts on what is important to patients, notably to reduce pain, anxiety, thirst, breathlessness and other distressing symptoms. Additionally, simplification will harmonise care, which will facilitate staff training. Simple care will form a cleaner baseline for observational and interventional research and thereby increase the likelihood of developing new diagnostics, risk scores and interventions that will be useful for future patients.

Summary

While it is tempting to be disappointed when an RCT reports that a new or established treatment does not have demonstrable beneficial effects, or even harms our patients, such information is critical and has undoubtedly contributed to the improved outcomes now experienced by critically ill patients. We must stop characterising such results as "negative trials" and instead celebrate the knowledge they provide and encourage all critical care practitioners to incorporate that knowledge into their decision making at the bedside.

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Compliance with ethical standards

Conflicts of interest
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