from prostate cancer is 3 percent and the lifetime risk of a diagnosis of prostate cancer is 16 percent, it is apparent that any approach that finds more cancers without quantifying the clinical significance of the detected disease will only increase overdiagnosis and overtreatment, as alluded to by Thompson et al. This, together with the absence of proof that PSA screening saves lives, should cause physicians to be circumspect about routinely recommending a prostate biopsy for men over the age of 50 years who have a PSA level of 4.0 ng per milliliter or less.

Although the value of PSA screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test, so that they can make an informed decision about the need for routine screening. The enthusiasm for screening in general in the United States suggests that most men will decide to be tested.

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Is Albumin Safe?
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The Saline versus Albumin Fluid Evaluation (SAFE) Study, reported in this issue of the Journal, heralds a new era in critical care marked by the large, simple, randomized trial popularized by cardiologists. In a study of fluid resuscitation involving nearly 7000 critically ill patients, the Australian and New Zealand Intensive Care Society Clinical Trials Group addressed one of the most fundamental and contentious issues in critical care. Questions about the merits and demerits of colloids as opposed to crystalloids in the resuscitation of seriously ill patients have smoldered for decades, sparked by a meta-analysis suggesting that albumin was associated with increased mortality and fueled by conflicting results from randomized trials. Individually and in the aggregate, interpretation of these findings has been challenging because of the systematic and random error inherent in the study designs and the frequent focus on surrogate rather than patient-centered outcomes.

The conclusion that albumin could increase the risk of death led to responses ranging from policies to limit albumin use, to claims that this interpretation was tendentious, to academic and industry counter-detailing, and to confusion at the bedside. Recognition that meta-analyses of small, older trials may yield findings that are discordant with those of newer large and rigorous trials provided the SAFE Study investigators the opportunity to ask the following question: In a heterogeneous
population of critically ill patients who require fluid resuscitation, what is the effect of 4 percent albumin versus 0.9 percent sodium chloride on 28-day mortality?

Randomization in the study was concealed. Generic packaging and formal testing ensured the blinding of the patients, clinicians, and researchers. Random error was minimized by the accrual of a sufficient number of patients to allow the detection of a 3 percent absolute reduction in mortality from a baseline rate of 15 percent, with 90 percent power. Compliance was excellent; more than 97 percent of patients received their assigned fluid. Contamination with nonstudy fluid occurred in less than 10 percent of the patients. The reported use of concurrent interventions was similar in the two groups; it is implausible that unreported concurrent interventions would be so prevalent, so powerful, and so unevenly distributed that they would invalidate the overall findings.

The results of the study challenge some polarized convictions. Mortality did not differ significantly between the patients assigned to albumin and those assigned to normal saline (relative risk of death in the albumin group, 0.99; 95 percent confidence interval, 0.91 to 1.09). Rates of secondary outcomes — survival time, organ dysfunction, the duration of mechanical ventilation, the duration of renal-replacement therapy, and the length of stay in the intensive care unit and in the hospital — were also similar.

To whom do these results apply? The characteristics of the patients included in the study reflect the research question posed and the effectiveness of the design chosen. Patients were eligible if clinicians judged that fluid was needed to treat intravascular volume depletion. One other sign of hypovolemia was required, such as a heart rate of more than 90 beats per minute, a systolic blood pressure of less than 100 mm Hg, a mean arterial pressure of less than 75 mm Hg, the need for inotropes or vasopressors, specific central-venous monitoring pressures, oliguria, or findings such as a capillary refill time of more than one second. Resuscitation generally involved the infusion of at least 250 ml of study fluid, followed by clinical assessment. Patients recovering from liver transplantation or cardiac surgery and patients with burns were excluded. More than 60 percent of the patients were mechanically ventilated. The average length of stay in the intensive care unit was approximately one week, and the average stay in the hospital was approximately two weeks. The results of the study apply to a diverse population of critically ill patients similar to those enrolled.

In the context of the overall results, what do the subgroup analyses suggest? The potential for specific fluids to help or harm specific populations was previously raised by a meta-analysis showing that among patients with trauma, those who received crystalloids had a significantly lower mortality rate than those who received colloids. Accordingly, trauma was a stratification variable in the SAFE Study. Subgroup analyses revealed no significant differences in mortality between patients who received albumin and those who received saline, but among the 1186 patients with trauma, albumin was associated with a trend toward increased mortality (relative risk of death in the albumin group, 1.36; 95 percent confidence interval, 0.99 to 1.86), possibly explained by the effect of trauma associated with brain injury (relative risk of death, 1.62; 95 percent confidence interval, 1.12 to 2.34). One hypothesis-generating subgroup invites further research: among 1218 patients with severe sepsis, albumin was associated with a trend toward reduced mortality (relative risk of death, 0.87; 95 percent confidence interval, 0.74 to 1.02). Inferences about subgroups are strongest when subgroups are few in number, are based on biologic mechanisms, and are established a priori and when the results are supported by indirect evidence. Therefore, cautious interpretation of these findings is warranted.

From the perspective of practice, some clinicians will point to the overall absence of harm associated with albumin in the SAFE Study and use it on the basis of pathophysiological rationale and favorable trends in selected studies. Others will conclude that without proof of benefit, routine use of albumin is hard to justify; for similar clinical outcomes at a lower cost, crystalloids may suffice in most circumstances. The use of albumin will reflect how clinicians interpret the point estimate for the overall treatment effect in the SAFE Study (which suggests equivalence, although proof of equivalence would require a different sample-size calculation), and the confidence interval (which is consistent with a 9 percent decrease and a 9 percent increase in mortality). Additional influences will include patient-specific conditions, clinicians’ preferences, perceptions regarding the safety of biologic fluids, availability, and cost. Whether decreased use of albumin, reported after the publication of a meta-analysis by the Cochrane Injuries Group Albumin
Reviewers,² will continue or reverse will be scrutinized from a policy perspective.

From the perspective of research, the affair with albumin in the intensive care unit is not over. Numerous questions based on the oncotic and non-oncotic biologic properties of albumin⁸ are being addressed. They include the effects of different doses and concentrations, such as rapid increases in oncotic pressure with 25 percent albumin. The combination of albumin and furosemide in hypoproteinemic patients with acute lung injury is under investigation.⁹ Also ongoing is a multinational, nonblinded trial comparing crystalloids (isotonic or hypotonic) and colloids (gelatin, starch, or albumin) in a heterogeneous population of patients in the intensive care unit (Annane D, Hôpital Raymond Poincaré, Paris; personal communication).

From the perspective of trial management, three aspects of the SAFE Study are noteworthy. First, screening and randomization were performed by bedside nurses and physicians. Second, recruitment was facilitated by an Internet-based system of randomization and took place 24 hours a day, 7 days a week. Third, a provision for delayed consent was used for 95 percent of the patients. Consequently, the rapidity of recruitment liberated substantial time for research coordinators to optimize the protocol implementation.¹⁰ Password-protected Internet-based data management helped to ensure patient confidentiality, allowed timely data verification, and offered participants the incentive of feedback about recruitment. Remarkably, the SAFE Study was completed ahead of schedule.

It is instructive to reflect on the road that clinical research in critical care has traveled. By 1995, approximately 1300 randomized trials in this field had been reported.¹¹ Of the 660 trials reported in two specialty journals, half enrolled fewer than 100 patients, and 10 percent were multicenter studies. Clinical research in intensive care has been transformed during the past decade. Currently, several national and international consortia address the pressing problems associated with critical illness. Key features of these consortia include a sense of mission to achieve shared goals and acknowledgment that such networks are much more than the sum of their parts.¹² Investigator-initiated, peer-review–funded trials in intensive care have grown from a small cottage industry into a major academic enterprise. Research priorities for such studies, in contrast to industry-initiated, industry-sponsored studies, are driven more by questions arising in practice than by the allure of new technology or corporate directives. Some research consortia also invest in the future, increasing public awareness of critical illness through fund-raising¹³ and through formal training of future investigators.¹⁴

The SAFE Study was a randomized, concealed, blinded trial that examined a ubiquitous intervention in the intensive care unit: intravenous fluid. Commendably conducted, carefully analyzed, and transparently reported, this study has raised the bar for future trials by using multidisciplinary implementation strategies and Web-based management and by demonstrating excellent protocol adherence in thousands of patients. The SAFE Study is not only a landmark trial; it is also a milestone for the discipline of critical care medicine.

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