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EDITORIAL

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Science, medicine and industry: are we getting out of the black hole in sepsis research?

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In this issue of *Intensive Care Medicine,* Finfer and colleagues describe an important new clinical trial which (re-)examines the effects of a not-so-new drug—recombinant human activated protein C (rhAPC)—on outcome in sepsis [1]. This publication is important because it describes—at an early phase—the basis for and protocol of a study, which will hopefully not only clarify but also potentially change clinical use of this drug. The decision to inform the intensive care community of the trial right from the beginning also motivates this editorial, which reviews some aspects of the complexity of the relationship and interactions in the triangle of three major players (but not always ideal partners) involved in pertinent clinical research: science, medicine and industry.

The primary objectives of each of the three stakeholders are quite different. The pharmaceutical industry wants to make profit, but is also very much interested in bringing new products to the market (necessary for its sustainable development) and in innovation (which improves its image in the eyes of society). Science is curiosity-driven, with the aim of furthering our understanding of human biology, physiology, and mechanisms of disease, also to discover better ways to treat disease. Finally, the objective of medicine is to help patients to get better quickly and to recover a good quality of life.

Naturally, the patient and society cannot be left out. They expect, if not cure, then the best possible care, and at an acceptable price. Society and the public also expect the major players in medical progress to demonstrate corporate responsibility, meeting the strictest ethical standards, ensuring the protection of patients' dignity and physical integrity, and respecting the principle of distributive justice with regard to the limited resources available for health care. This also includes sharing access to knowledge and benefits from novel interventions.

There is still much that we do not know about sepsis. It is a very complex syndrome, with many different presentations and several forms of clinical evolution, which makes understanding it more difficult and a standard approach to management elusive. Sepsis is also a good example of the essential steps in "translational research". More than for other diseases, our understanding of sepsis has evolved because of multiple journeys from bedside to bench and back. Many areas of basic science and a variety of clinical specialties have contributed to major developments in the field. Fortunately, the role of industry has not been limited to supporting the clinical aspects of research and testing of new drugs or devices; the financial support provided by industry for elucidation of basic mechanisms has been significant. Active intellectual and financial relationships between industry and its partners in research and health care have brought significant progress to science and patient care. However, there is a clear need for better rules, improved disclosure and management principles [2–4].

Now, in their new clinical trial, Finfer and colleagues—all renowned specialists in the field of intensive care—and representatives of industry have seized a unique opportunity to make a model case, not only for efficient collaboration, but also for providing better overall transparency from the beginning of a study to the very end, up through the publication of all relevant results. Clinicians count on the complete objectivity promised by investigators and industry, and the availability of all results, to bring them desperately needed clarification in the treatment of septic shock. Ultimately, the ICU team wants a clear answer to the question of which patients—if any—benefit from rhAPC.

Mutual trust between medicine, science and industry is essential but not free from conflicts of interest, since the scientific community and industry depend on each other to such a great extent [5]. Society and the media are suspicious of collaborations between industry and the medical and scientific communities; they often see conflicts of interest, which do not seem evident to those directly involved. This mistrust results, for example, in articles "accusing the drugmakers of deceiving the public, manipulating doctors and putting profits before patients" [5]. It is up to medicine to convince all interested parties—scientists, industry, and society—that it does the best it can for the patient. Today society is more critical of science and medicine when these seem not to respect the limits set by common sense for transparency and financial disclosures.

A good way to provide support for the industry–science–medicine triangle in light of public (mis)trust is to enforce guidelines established by neutral bodies, defining good collaboration, conflicts of interests and integrity in science. Such guidelines exist [6, 7], and the general adherence to them must be made more widely known to the public. At the same time, controlling has to be improved and non-adherence must be clearly sanctioned.

Intensive care medicine is a young specialty, and large-scale randomized controlled trials (RCTs) in this domain have a very short history. Before the 1980's, practically no large RCTs were performed. By 1990, the number of intensive care RCTs published annually had reached 50 (PubMed search for "intensive care OR critical care", "humans, randomized controlled trial"), and in 2000, for the first time more than 200 articles per year could be found with these search terms. It is therefore clear that the bulk of clinical intensive care medicine practice is not evidence-based, but rather based on physiological and pathophysiological concepts and craftsmanship.

The quest for evidence-based treatments for critically ill patients has led to proliferation of RCTs. Unfortunately, most RCTs in intensive care medicine have produced negative results, including increased mortality from interventions expected to improve outcomes, and non-reproducible results of trials that have changed clinical practice [8–23]. Also, the design and interpretation of several benchmark clinical RCTs have been questioned and heavily debated [24–28].

The frustration of evidence-based medicine-driven scientists and clinicians is not surprising, and it is understandable that the intensive care medicine community may be ready to jump on any bandwagon resulting from a single positive RCT. This frustration is the likely explanation for the rapid acceptance and widespread promotion of such single-center trial findings as tight glucose control [22] and "early goal-directed therapy" [29] in sepsis. In marked contrast to this enthusiasm, the positive results from the PROWESS study [17], a large, international multicenter RCT on recombinant human activated protein C (rhAPC) in sepsis, have been applied in clinical practice with substantial hesitation, despite the high-profile publicity and aggressive marketing surrounding the results and the inclusion of the use of rhAPC in the (also controversial) Surviving Sepsis Campaign treatment guidelines [30].

What can explain this apparent reluctance to translate into clinical practice the results of a large, international, multicenter RCT, a prime example of the kind of evidence praised by evidence-based medicine? Some would argue that it is the costs. Yet, although costly in comparison to many common drugs, rhAPC is not particularly expensive when compared to the overall costs of intensive care or to use of such common interventions as modern coronary artery stents. Others would argue that the aggressive marketing may have backfired. While these issues may certainly contribute, a much more complex, and in fact reasonable, explanation seems likely.

Intensive care clinicians are uncomfortable with the specific problems related to RCTs in intensive care patients with sepsis. Although it is a rapidly lethal condition, sepsis is a syndrome rather than a well-definable disease. The clinician recognizes the diversity of clinical problems and comorbidities that are common in patients with sepsis, and is likely to be reluctant and uncomfortable in administering a drug with a broad spectrum of biological effects and potentially serious, even life-threatening side effects. It does not help that the exact pathophysiological mechanisms of the expected benefits of rhAPC in sepsis are unclear and subject to debate.

Not only clinicians but also regulatory authorities seem to share this reluctance. The United States Food and Drug Administration (FDA) approved rhAPC in the midst of debate, and attached a severity score in the drug's label—an unprecedented concept, given that severity scoring systems have never been validated for this purpose. The European authorities also attached a severity-of-disease indicator (organ system failure) in the

label, and chose to give a time-limited approval, later insisting that a confirmatory trial was necessary. This has now resulted in the launch of the PROWESS-shock study.

All this debate and controversy has finally had a sobering effect on the translation of results from clinical trials into clinical practice. In the era of large "pivotal" RCTs, it is often forgotten that reproducibility is the crucial issue in evaluating any scientific evidence. In order to justify fundamental changes in current practice, multiple positive RCTs are necessary. When the results of all or most of the available research points in the same direction, it is much more likely that the finding also holds true when the intervention is applied outside of strictly controlled clinical trials. In the end, it is up to the clinician to ask: How well do the study setting and patient selection represent those patients that I am considering for the intervention? How well does the known risk-benefit profile apply to my patient population [31]? Am I convinced that there is more benefit than potential harm?

Meanwhile, the sponsor of the PROWESS-shock study must be painfully aware of the specific problems related to large RCTs in the critical care setting: patients with rapidly lethal conditions, the poorly definable syndromes rather than diseases present in most septic patients, the difficulties in assessing the severity of such syndromes, the interacting treatments, and the at best marginally understood interactions between physiology, pathophysiology, and concomitant treatments. If the results of the PROWESS-shock trial do not confirm the results of the original PROWESS trial, it is unlikely that industry will continue to expend money and effort on evaluating rhAPC in sepsis. This would have potential far-reaching consequences in terms of the readiness of industry in general to invest in critical care trials.

In addition to efficacy, one of the most important concerns with rhAPC has been safety, especially the risk of bleeding. Efficacy trials may not reveal the full risk profile of a drug. The risks of bleeding may be higher in clinical practice, where the spectrum of patients may be wider than in the strictly controlled clinical trial setting. It is also conceivable that different combinations of drugs interfering with the coagulation system may modify the additional risk of bleeding caused by rhAPC. The available data suggest that the risks of bleeding that accompany the use of rhAPC may indeed be higher than originally estimated from the RCTs.

Concerns over safety issues not revealed in RCTs powered for efficacy is nothing new. Of the new drugs submitted to the FDA from 1993 to 2004 and approved by 2005, 11 registered drugs were withdrawn from the market for safety reasons in the US [32]. The current study adds a sizeable group of patients with the highest severity of illness, whereas the previous studies covered a wide spectrum of severity of illness; it is therefore very well conceivable that the side effect profile may be different.

Safety monitoring in rapidly lethal diseases is difficult, and the PROWESS-shock trial focuses on a patient subgroup with especially lethal disease. Considering the safety concerns related to the use of rhAPC, maximizing safety monitoring would have been preferable. This would include—in addition to the "normal" procedure of submitting the study to a data safety monitoring committee—an unblinded safety assessment. The current study design allows the data safety monitoring committee to request an unblinded review, but such a review is not mandatory. Many intensivists—including the authors of this editorial—are convinced that the disadvantages of blinded evaluation outweigh the advantages. In our view, unblinded safety monitoring, independent of the request of the data safety monitoring committee, should have been included in the protocol for the PROWESS-shock trial (see for example [33]).

One of the major issues in industry-sponsored research is the scientific community's lack of access to the data. In many instances, investigators' access to the data is restricted as well, and the pharmaceutical industry has even been known to restrict investigators' rights to publish. Meanwhile, the scientific community has a track record of naivety and willingness to sign contracts that restrict their rights. Despite the fact that scientific journals commonly request authors to confirm that they have had full access to the data and that they agree with the analysis and interpretation, true full and unrestricted access to industry-supported study data is rather a rare exception. This is a major concern for many reasons, including, for example, independent verification of study results, publication bias of negative results, and lack of possibility to address potential safety issues in accumulating data, just to name a few.

The investigators of the PROWESS-shock trial have made a laudable effort to introduce an improved model of collaboration between science, medicine and industry. This approach could help to get us out of the image of a Bermuda triangle, where benefits of research and resources for health care disappear in a black hole or the wallets of a few. All parties involved have taken major steps. The ultimate goal is a platform with open access for the entire scientific community. Only by working together—with trust and transparency—can we hope to solve the riddle of sepsis in the decades to come.

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