

spond quickly and affirmatively, and they need the resulting reconstructive procedure to be fundamental, rather than cosmetic.

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Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly

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Practice guidelines approved by expert panels are intended to standardize care in such a way as to improve health outcomes. In recent years, the developers of such standards have started grouping evidence-based interventions into “bundles,” on the theory that inducing physicians to follow multiple recommendations written into a single protocol has a measurable effect on patients’ outcomes. As a side effect, bundled performance measures are ready-made for use in pay-for-performance initiatives, which can base reimbursement on compliance with all the components.

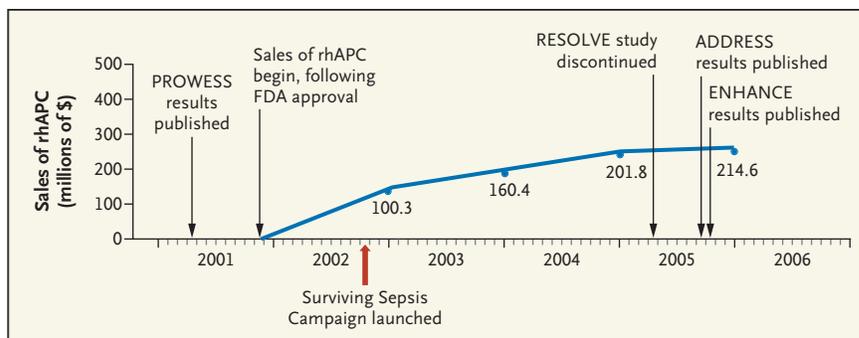
Unfortunately, the development of such clusters is vulnerable to manipulation for inappropriate — and possibly harmful — ends. Seeing in these bundles a potentially powerful vehicle for promoting their products, pharmaceutical and medical-device companies have begun to invest in influencing the adoption of guidelines that serve their own financial goals. A case in point is the development of guidelines for the treatment of sepsis, which was or-

chestrated as an extension of a pharmaceutical marketing campaign.^{1,2} Although its advocates viewed this effort as an important approach to reducing sepsis-related mortality, the campaign appears to have usurped guideline development for commercial purposes, possibly compromising highly regarded, third-party arbiters of medical quality in the process. Such intrusion into an initiative to benefit public health is of particular concern in this instance, since the drug incorporated into the performance measures was endorsed on the basis of a single controversial phase 3 trial that was still being called into question by additional studies even as the committee did its work.

In 2001, the Food and Drug Administration (FDA) approved Eli Lilly’s Xigris (recombinant human activated protein C, or rhAPC, also known as drotrecogin alfa [activated]) for the treatment of sepsis. This approval was based primarily on a single phase 3 randomized, controlled trial — the Recombinant Activated Human Protein C Worldwide Evaluation in

Severe Sepsis (PROWESS) study, published the same year — which showed a significant overall survival benefit at 28 days. The FDA acknowledged that there was controversy surrounding this decision, and half the members of the agency’s advisory panel, pointing to methodologic and other important problems with the PROWESS study, voted to require that a confirmatory trial be performed before approval was granted. In its approval statement, the FDA recommended using rhAPC in patients deemed, on the basis of an Acute Physiology and Chronic Health Evaluation II score of 25 or more, to have a particularly high risk of death; since this criterion had not been prospectively validated, the agency asked Lilly to perform additional testing in selected subgroups. In the face of such uncertainty, initial sales of rhAPC fell short of market expectations (see timeline).³

To improve sales of rhAPC, in 2002, Lilly hired Belsito and Company, a public relations firm, to develop and help implement a three-pronged marketing strate-



Timeline of Controlled Trials of rhAPC, Regulatory Actions, Yearly Sales, and the Marketing Initiative by Eli Lilly.

The Surviving Sepsis Campaign consisted of three phases — an initial one defining the need to treat sepsis, a second one developing treatment guidelines, and a third one developing and implementing performance bundles based on the guidelines. The four data points show end-of-year sales. The company had predicted annual sales of \$300 million to \$500 million.

gy.¹ First, the product's sales were to be supported by marketing initiatives targeted to physicians and the medical trade media.¹ Second, because rhAPC was relatively expensive, word would be spread that the drug was being rationed and physicians were being “systematically forced” to decide who would live and who would die.^{1,3} As part of this effort, Lilly provided a group of physicians and bioethicists with a \$1.8 million grant to form the Values, Ethics, and Rationing in Critical Care (VERICC) Task Force, purportedly to address ethical issues raised by rationing in the intensive care unit.³ Finally, the Surviving Sepsis Campaign was established, in theory to raise awareness of severe sepsis and generate momentum toward the development of treatment guidelines.

The first phase of the Surviving Sepsis Campaign was introduced at an October 2002 meeting of the European Society of Intensive Care Medicine (ESICM). In the second phase, launched in June 2003, international experts in critical care and infectious

diseases were convened to create guidelines for sepsis management, which were published in *Critical Care Medicine* in March 2004.⁴ Lilly provided more than 90% of the funding for these two phases, and many participants had financial or other relationships with the company.^{1,4} According to the Council of Public Relations Firms, Belsito helped to assemble the VERICC Task Force and launch the campaign, and initiated a media-outreach program to “raise awareness” of alleged rationing in severe sepsis with the intent of generating demand for rhAPC.¹

Campaign participants might argue that, regardless of Lilly's concerted efforts, the guidelines were not influenced by the company and represent best practice based on the evidence that was available — largely from randomized, controlled trials.⁴ Although such trials represent the gold standard of medical evidence, overreliance on them in the construction of guidelines has a tendency to favor new drugs and devices, which typically undergo at least one such trial in order to

obtain government approval. In this instance, that reliance meant that rhAPC was given a highly favorable rating (grade B), whereas established therapies for sepsis (such as antibiotics, fluids, and vasopressors), though included in the recommendations, received lower ratings (grade D or E), because most had not undergone randomized, controlled trials owing to a lack of equipoise.

This imbalance is made more troubling by the campaign's failure to discuss persisting concern about rhAPC, which has been reinforced by recent trials. After the PROWESS study, which had demonstrated an increased risk of serious bleeding, two other controlled trials — the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) study and the Resolution of Organ Failure in Pediatric Patients with Severe Sepsis (RESOLVE) study — both of which were terminated early because they were deemed unlikely to show a significant difference in their primary end points, confirmed that increase in risk and resulted in warnings submitted by Lilly to the FDA regarding the use of rhAPC. Although the results of the ADDRESS study were reported at the October 2004 ESICM meeting, no mention of the study was included in a supplement to the Surviving Sepsis Campaign Guidelines published the following month in *Critical Care Medicine*. Results from one open-label trial, the Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) study, published in October 2005, indicated that the risk of bleeding associated with rhAPC might actually be greater than originally esti-

mated. Although data from the ENHANCE trial were available and are included in the guideline supplement, the possible magnitude of this increased risk (a 28-day incidence of serious bleeding of 6.5%, as compared with 3.5% in the PROWESS study) is not noted. Moreover, the efficacy of rhAPC has not been prospectively demonstrated in the patient population for which the drug is currently recommended.

Eleven professional societies are cited as sponsors of the Surviving Sepsis Campaign Guidelines. The Infectious Diseases Society of America (IDSA), however, declined to endorse them. According to Naomi O'Grady, the physician who chaired the IDSA's Standards and Practice Guidelines Committee from 2002 to 2005, the organization found fault with the manner in which the guidelines were developed, the use of a suboptimal rating system, and their sponsorship by a drug company. The peer-review process conducted by the IDSA might provide a model for an objective system of rating proposed guidelines in the future. But in this case, even the fact that the society decided not to endorse the recommendations is not widely known. According to Dante L. Landucci, an intensivist at East Carolina University, *Critical Care Medicine*, which published the guidelines, removed mention of the IDSA's rejection from his invited editorial on the subject that appeared in print 3 months after the guidelines did.

As part of the third phase of the campaign, Lilly awarded unrestricted grants for an "Implementing the Surviving Sepsis Cam-

paign" program.⁵ The main goal of this phase, launched in mid-2004, is the creation of performance bundles based on selected recommendations from the campaign guidelines. Again, many participants have self-reported financial or other relationships with Lilly.^{4,5} Despite the persisting scientific controversy surrounding its safety and efficacy, rhAPC is included in one of these performance bundles. Neither the campaign's manual on bundle implementation nor a cover letter from the president of the Society of Critical Care Medicine mentions the ADDRESS and RESOLVE trials or the warnings they precipitated.⁵ In formulating and promoting the bundles, the campaign sought to collaborate with public, not-for-profit arbiters of the quality of health care, including the Voluntary Hospital Association, the Institute for Healthcare Improvement, and the Joint Commission on Accreditation of Healthcare Organizations.^{2,5}

Implementation of the bundles is being advocated nationally in workshops organized under the auspices of the Society of Critical Care Medicine and funded by Lilly. Furthermore, the campaign has lobbied state governments to adopt the bundles. Efforts to institute these measures internationally are being promoted in a program called the "Surviving Sepsis Campaign Roadshow," also subsidized by Lilly. In addition, the company funds *Advances in Sepsis*, a widely distributed periodical that publicizes the campaign. These activities continue unabated amid increasing calls for a new, prospective study of rhAPC.

When properly formulated and

applied, practice guidelines and performance standards hold the promise of improving patients' outcomes. Professional societies and other stakeholders must work together to promote a consistent guideline-development process, a robust rating system for guidelines that is applicable to all subspecialties, and a policy that prohibits the pharmaceutical and medical-device industries from directly or indirectly funding or influencing practice standards. The challenges involved in producing first-rate guidelines and performance standards are only exacerbated by the intrusion of marketing strategies masquerading as evidence-based medicine.

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