Microglial cells and astrocytes in the brain may play a role in the behavioral changes due to systemic inflammation induced by critical illness and are related to the development of dementia as well. These neuroinflammatory mechanisms could explain the higher level of markers for cerebral damage associated with delirium. Future studies should investigate the effect of multicomponent interventions to prevent delirium with a goal of reducing the incidence of cognitive decline after hospitalization.

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In Reply: We agree with Drs van Munster and de Rooij that delirium is likely an important factor in the pathway between acute or critical illness and cognitive decline in older patients. Not only has delirium been shown to be associated with higher mortality, longer length of stay, and greater cost in critically ill patients, a number of studies have demonstrated the association between delirium and long-term cognitive outcomes. In addition to the evidence that inflammation may play a role in the pathophysiology of both delirium and dementia, patients with an apolipoprotein E genotype associated with dementia (ApoE4) are at greater risk for delirium when critically ill. This also supports a link between mechanisms leading to delirium and those leading to long-term cognitive impairment.

We are interested in identifying factors during critical illness that may convey risk of long-term impairment, both to identify potential targets for intervention and to improve understanding of possible mechanisms for the association. Unfortunately, we are unable to explore the relationship between delirium and cognitive outcomes in our study cohort, since one limitation of using administrative data is the inability to ascertain which hospitalizations of study patients were complicated by delirium. We agree that studies of interventions aimed at reducing the occurrence of delirium should include long-term cognitive impairment as an important patient-centered outcome. Furthermore, we advocate increasing use of validated tools such as the CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) for assessment and documentation of delirium in the clinical care of critically ill patients. Future observational studies and perhaps patient care will benefit from more reliable detection of delirium.

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Registering Results From Clinical Trials

To the Editor: The Commentary by Mr Miller highlighted the importance of public access to clinical trial protocols in the context of results disclosure on registries such as ClinicalTrials.gov. We want to emphasize 3 additional issues to consider in the path toward increased transparency in clinical trials research.

First, public access to the full original protocol and subsequent amendments is critical to the proper evaluation of results and the identification of misreporting that may occur in approximately half of industry and nonindustry trials. However, only trial sponsors and the US Food and Drug Administration (FDA) have access to protocols and to results for studies submitted as part of a new drug or new use application. These 2 bodies cannot reliably help patients and clinicians tailor health care decisions: sponsors have inherent conflicts of interest, and the FDA approval process requires only that trials demonstrate superiority to placebo rather than comparative effectiveness. Therefore, protocols should not be withheld from clinicians who prescribe and patients who are consumers of drugs and other technologies.

Second, posting of trial results and public availability of protocols should be ensured independent of market status. The dissemination of results and protocols for all trials is necessary to advance knowledge and fulfill ethical responsibilities to study participants. These principles apply regardless of whether a clinical trial evaluates a new intervention or a new use of a previously approved intervention. Valuable data relevant to future research and current clinical practice would be lost if trial results and protocols relating to unapproved interventions or off-label uses re-
mained unavailable. These principles also apply to nondrug interventions and all types of trial designs.

Third, public access to protocols will only be useful if the description of trials in protocols is complete, accurate, and transparent. Many protocols do not address key issues such as describing their primary outcomes, analysis plans, and other important methodological items. There is a need for evidence-based guidance to help ensure that protocols contain the requisite information to enable critical appraisal of trial results.

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To the Editor: In response to the Commentary by Mr Miller on registering clinical trial results, we believe that transparency also concerns the patients who participate in a trial. Most of the participants want to know the study results despite their potentially negative emotional effect. Even if the Internet is not the preferred source of information for those patients, it could help to routinely share results with participants. A narrative and a lay summary might be posted on ClinicalTrials.gov.

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In Reply: The points made by Dr Chan and colleagues are important for both well-informed treatment decisions in the clinic and the progress of medical research generally. The recent systematic review by Bassler et al of inflated treatment effects in trials stopped early for benefit demonstrates the importance of prespecified stopping rules that require a significant number of events before stopping. It shows the need for full access to the protocol, including prespecified stopping rules, to independently assess the accuracy and reliability of the reported treatment effect.

Chan et al comment that the FDA generally does not require substantial evidence of a new drug's efficacy compared with drugs previously approved by the FDA for the same or a similar indication. If a placebo control would be unethical, the FDA does require an appropriate active control. Temple and Ellenberg are correct that active control trials are sometimes difficult to interpret, but this must be balanced against the equally valid point that FDA-approved comparative efficacy data are needed for sound clinical decisions. Under the Kefauver-Harris Drug Amendments of 1962, the FDA has broad discretion to require active controls (including when a placebo control would be ethical) and to require that the FDA-approved labeling of a drug include comparative efficacy data. An important question is why the FDA has not used this authority more often.

Drs Mancini and Reynier correctly emphasize the importance of communicating trial results to patients, especially the participants in a trial. The US Congress has required the National Institutes of Health to include a requirement that the sponsor of a trial post a summary of the trial and its results “written in non-technical, understandable language for patients” if this can be done in a way that does not mislead patients or promote a drug for an unapproved use.

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Registering Findings From Deep Brain Stimulation

To the Editor: In their Commentary, Drs Schlaepfer and Fins argued for starting a registry for deep brain stimulation, similar to the various registries for randomized controlled trials. The aim of the registry would be to prevent media attention for chance successes. However, the authors do not de-