We also have two minor comments concerning the article by Mashour *et al.*[1] and the accompanied editorial.[8] On the basis of the detailed description on page 719, the most important principle of randomization and the randomized controlled trial paradigm may have been breached; in a randomized trial, the investigator should not know the treatment/intervention allocation before patient recruitment. Or have we misunderstood the procedure? In addition, the editorial included a funny flaw: BIS spectroscopy. Surely, we are not able to *scope* anything with BIS.

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To BIS or Not to BIS

To the Editor:

I read with interest the study by Mashour *et al.*[1] The authors are to be congratulated for having performed this large randomized trial to answer an important question regarding the utility of bispectral index monitor and comparing that to minimum alveolar concentration level alarm system.

There are few points that warrant clarification. First, the author included patients who received total intravenous anesthesia. However, the details of this subgroup of patients were not provided. The method of determining the minimum alveolar concentration level in the no bispectral index total intravenous anesthesia patients, the alarm limits, and the incidence of awareness in these patients were not described.

Second, the inter-rater agreement using Fleiss κ statistic for the three blinded assessments of awareness showed fair agreement (0.25). Can the authors comment on the low level of agreement and provide the confidence interval for κ?

Third, 36% of patients did not have bispectral index data recorded because of technical issues. While this could provide a third arm for comparison, it may also create some bias. Providers who did not receive an alarm might have decreased vigilance as they could have depended on the alarm system. Adding a third arm of routine care in the design might have provided valuable information.

Finally, it would have been interesting to learn more about the 19 definite awareness cases in this large sample which could help in refining the characteristics of high-risk patients.

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In Reply:

We thank Dr. Myles for his thoughtful comments on our editorial[1] and his contribution to the field of anesthesiology in general and comparative effectiveness research (CER) specifically. The points, including the disagreement with our categorization of the discussed trials, are well taken and are representative of a wider discussion about the question of what actually constitutes CER and what methodologies should be used to achieve it.[2,3] Although the most commonly used definition in the United States today is that put forth by the Federal Coordinating Council for Comparative Effectiveness Research in 2009,* it can be argued that principles

* FCCCER (Federal Coordinating Council for Comparative Effectiveness Research). "Report to the President and Congress." Washington, DC: U.S. Department of Health and Human Services, June 2009. Available at: www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf. Accessed January 4, 2013.

of CER have been followed in many other countries as early as the 1800s.[2]

In this context, we would like to state clearly that our intent was far from suggesting that the studies discussed and conducted by Dr. Myles and his colleagues do not conform to CER, because they clearly do individually and collectively, but rather to highlight an exciting evolution within anesthesia research that has been and continues to be under represented within CER. Although the intervention studied by Mashour *et al.*[4] may not currently represent "common" practice, the use of anesthesia information management systems and related technologies is rapidly increasing throughout institutions worldwide with novel applications emerging at increasingly faster rates. Therefore, it is without a doubt that technology will influence the way we practice anesthesia today and in the future, demanding that these advances have to be tested against traditional practice before they become or can become common place. If the goal of CER is to maximize efficacy, effectiveness, and efficiency in our healthcare system, we should not be bound by traditional definitions when judging the value of the results of a study and perhaps even expand such criteria as to not risk them becoming obsolete.

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In Reply:

We greatly appreciate the interest of Drs. Myles, Scheinin, Långsjö, and Helwani in the Michigan Awareness Control Study (MACS).[1] We are delighted that the study provoked a wide range of commentary from the semantics of clinical research terminology to the fascinating developments in the neuroscience of consciousness and anesthesia.

Dr. Myles states categorically that the methodology of MACS is not consistent with comparative effectiveness research (CER), referring to the Institute of Medicine's definition for support. The Institute of Medicine defines CER as:

> *…the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.*[2]

The report goes on to state that the "key elements of this definition are the direct comparison of effective interventions, the study of patients in typical day-to-day clinical care, and the aim of tailoring decisions to the needs of individual patients." MACS resulted in the *generation of evidence* by a *direct comparison* of the *benefits* of alarms based on the *alternative methods* of minimum alveolar concentration and the Bispectral Index (BIS), to *monitor* and *prevent* the *clinical condition* of intraoperative awareness with explicit recall. Both end-tidal anesthetic concentration monitoring (B-Unaware trial)[3] and BIS (B-Aware trial)[4] had been previously demonstrated to be *effective interventions* that can prevent awareness and improve *delivery of care* in the intraoperative setting. The interventions were triggered by physiologic or pharmacologic data derived from *individual patients* across multiple care settings. After the investigators implemented the alerting algorithm through the perioperative information system at the beginning of the study, hundreds of nurse anesthetists, residents, and attending anesthesiologists engaged in their *typical day-to-day clinical care*, without any requirement on their part to set or optimize conditions for study success. We acknowledge that aspects of MACS and other awareness trials are subject to interpretation with respect to the designation of CER. However, Dr. Myles presents no compelling arguments for why MACS does not meet the essential definition of CER proposed by the Institute of Medicine.

Although we do not agree with his assertion, Dr. Myles furthermore states that the methodology of MACS is not generalizable outside of the "very specific setting" of the trial. It is therefore surprising that Dr. Myles incorporated the results of MACS into a meta-analysis, a statistical technique that relies on generalization. In a textbook on statistical methods,[5] Drs. Myles and Gin propose that a meta-analysis should only include trials that have "*similar patient groups, using a similar intervention, and measure similar endpoints*." Recognizing these constraints, we have attempted a synthesis of evidence regarding prevention of intraoperative awareness in a Clinical Commentary published recently in this journal.[6] In agreement with Dr. Myles's caveats about inclusion criteria for meta-analyses, we did not believe that the meta-analytic approach was appropriate to summarize the findings of the major awareness prevention trials. Specifically, we were concerned about disparate patient groups (high-risk patients *vs.* unselected surgical patients), different anesthetic techniques (volatile-based *vs.* total intravenous anesthesia), dissimilar interventions (routine clinical practice *vs* an alternative protocol in the control groups), and inconsistently defined endpoints (credible awareness report *vs* dreaming