REPORTS OF SCIENTIFIC MEETINGS

James C. Eisenach, M.D., Editor

Workshop on How to Perform Clinical Outcome Studies. University of Münster, Münster, Germany, May 22–23, 1997.

Our speciality is witnessing an increasing number of reports of clinical trials that attempt to examine risks and benefits from various postoperative analgesic regimens, most of which are inconclusive because of faults in study design. The purpose of this workshop involving 24 individuals from 6 countries and organized by Professors Hugo Van Aken (University of Münster) and Michael Todd (University of Iowa) was to examine the reasons for these weaknesses and the central issues in the design of such clinical trials. Three major questions were addressed:

1. What are reasonable primary outcome variables? Central to this discussion was the need to define one or possibly two primary variables that are considered to represent the essential benefit that could be accrued by the analgesic regimen. Although pain relief itself should be assessed in such trials, it should only be considered a primary variable if it is hypothesized that traditional methods of pain control are inadequate. Two types of primary outcome variables were discussed for these clinical trials. One type, appropriate to high-risk patients, is major morbidity or mortality. The consensus appeared that surrogate measures should not be used. For example, although there may be a relationship between heart rate and myocardial ischemia and between myocardial ischemia and myocardial infarction after surgery, if the major morbid event to be examined is myocardial infarction, then use of either heart rate or ischemia should not be used. Rather, myocardial infarction itself should be the primary outcome variable.

A second type of outcome variable discussed was hospital stay. It was argued, particularly by Dr. Kehlet (Hvidovre University Hospital, Denmark) that duration of hospital stay could be a very appropriate and important primary outcome variable. A multimodal approach to postoperative pain management, including regional anesthesia with combination local anesthetic–opioid therapy, early ambulation, and early enteral nutrition might potentially reduce postoperative morbidity. An appropriate control group would be parenteral opioid therapy using patient-controlled analgesia. Early mobilization and early enteral nutrition would be attempted in this group. Although duration of hospital stay itself was considered an extremely important economic variable, several problems were identified in its use within and among institutions because the decision to discharge a patient is reliant on so many factors and traditions that are difficult to control. Such studies might be difficult to perform in a randomized design, which was thought to be an essential ingredient in trial design (to be discussed).

A variant of this type of outcome variable is the concept of "fast-tracking." For the patient undergoing cardiac surgery, it may mean early extubation or bypassing the intensive care unit, whereas in the ambulatory setting, it implies bypassing the postanesthesia care unit. In the area of abdominal surgery, earlier discharge has been achieved by implementing protocols involving early alimentation, ambulation, and aggressive multimodality pain management. Increasingly, physicians are being asked why any noncritically ill patients need to be in the hospital after surgery. Clearly, studies are needed to identify the factors that preclude earlier discharge after major surgery.

2. What operations or patient populations should be studied? Two hypotheses were generated regarding which operations should be studied to determine the role of pain management in outcome of postoperative patients. One possibility would be to study a high morbidity group like aortic (*i.e.*, abdominal aortic aneurysm) surgery or elderly patients undergoing surgical repair for hip fracture. A reduction in the relatively high incidence of morbidity in these groups might be readily demonstrated with a multimodal approach to pain management. A preliminary goal of a reduction in morbidity by 25–80% was suggested, perhaps requiring only 60–100 patients to demonstrate this. Preliminary data should be gathered before power analyses. Populations with a lower incidence of morbidity, as in patients undergoing thoracotomy, colectomy, and hysterectomy, were considered. With a lower incidence of morbidity, perhaps the same 25–80% reduction in morbidity could be achieved, but a greater number of patients (200–500) would be studied.

3. Must these trials be randomized and blinded? Randomization of subjects in clinical outcome trials can be difficult to accomplish, although the impact of a study depends on rigorous design. This issue was clearly illustrated by Tim Brennan, M.D., (University of Iowa) in a comparison of several published studies with interesting outcome data. Those that were designed as randomized trials had far greater impact on the academic community than those that were not, even though the data were clinically interesting in the latter. Blinding or masking should also be considered in the study design, but this factor is not as important as randomization and may even be associated with ethical concerns. In some trials, blinding may be impractical and cumbersome, and the outcome variables being measured may be unaffected by blinding of methods. Although sham techniques can be used (*e.g.*, epidural catheters with reservoirs taped to the back), use of sham techniques that could cause injury to the patient cannot be justified. In cases where the outcome variable(s) might be affected by the use of blinding, the number of patients studied can be increased to compensate for this effect. The ethics of sham therapy should be carefully considered when designing an outcome trial. To provide titration of pain relief in the postoperative period, the acute pain service should remain unblinded. If the trial is blinded, the efficacy of the blinding should be confirmed at the end of the study. The ethics of blinding in pain trials were discussed by A. A. Spence, C.B.E. (The University of Edinburgh, UK).

Early termination of a trial and interruption during the trial to analyze data are interesting problems that should be considered in the study design. Denise Wedel, M.D., (Mayo Clinic) discussed various scenarios that might warrant interim analysis of data, including strongly positive findings, adverse effects, and lack of effect of a trial therapy. The point was made that early termination or interim analysis, although sometimes justified, require rigorous statistical analysis to maintain validity in the reported results.

Paul White, M.D., (Southwestern Medical Center, The University of Texas) discussed the problems with obtaining informed consent from participants in outcome trials. The form and timing of consent are determined by local and national regulatory bodies. Informing the participant without bias or coercion is a challenging but necessary aspect of performing these trials.

In summary, this workshop focused on the need for investigators to carefully define one or two primary outcome variables, avoid surrogate measures, and define the population appropriate for the question being asked in postoperative analgesic trials. Not only should the question be clearly defined, but a proper power analysis should precede implementation of the trial to assure that the expense and effort required for such studies has a reasonable likelihood of successfully answering the question.

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Other invited workshop participants included: From Germany: Drs. G. Broder, L. Hertle, Th. Prien, N. Senninger, R. Toellner, and K. Uberla of Munster; R. Grundmann, Melsungen; J. Jage, Mainz; K. Peter, Munchen; J. Schwarz, Neu-Isenberg; and H. Wulf, Kiel. From the United Kingdom: Dr. H. McQuay, Oxford. From France: Dr. P. Coriat, Paris. From the United States: R. Christopherson, Portland; and C. Meinert, Baltimore.