

kidneys from expanded-criteria donors who have acceptable characteristics (age, serologic results, creatinine levels, biopsy results, and pulsatile flow).¹³ Such a system can reduce the cold-ischemia time (the time between procurement and transplantation of the organ) and can thereby facilitate the identification of a suitable recipient for a kidney from an expanded-criteria donor.

We are confident that the transplantation community can change the current situation — in which 40 percent of kidneys from expanded-criteria donors are discarded. Innovative strategies can be developed to account for the quality of the potential donor's kidney and the potential benefit to the recipient, and an efficient system of allocation can be put into place that will enhance the opportunities for successful transplantation.

Dr. Delmonico is the president of the OPTN and UNOS. Dr. Burdick is the director of the Division of Transplantation of the Health Resources and Services Administration. No other potential conflict of interest relevant to this article was reported.

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The Value of Phase 4 Clinical Testing

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Since its inception in 1988, the Multicenter Study of Perioperative Ischemia Research Group has examined a number of critical issues concerning the outcomes of cardiac surgery and anesthesia. The group's database is a powerful research tool. Its power derives from the high quality of the participating institutions, the capability of these institutions to recruit a large number of patients, and an absence of potential conflict of interest, in part due to the large number of participating institutions and investigators.

In this issue of the *Journal*, Mangano et al.¹ report the findings from a large clinical database built on the data-collection efforts of this group in the United States, Canada, and else-

where. On the surface, this study might appear to be of interest only to those in the specialty fields of cardiac surgery and cardiac anesthesia. However, the importance of this study goes beyond the specific findings of the use of aprotinin to limit blood loss in patients undergoing cardiac surgery. Surgeons and anesthesiologists have long questioned whether the use of aprotinin increases the risk of renal dysfunction and thrombosis.² As a consequence, their use of this drug has ranged from use in all patients to minimize postoperative bleeding to use only in patients who have a high risk of substantial postoperative bleeding.

There are two primary reasons why aprotinin

is not used in all patients undergoing cardiac surgery: cost and potential risks. Some surgeons and anesthesiologists who use the drug have been concerned about its potential risks since it was first approved for clinical use; yet until the report by Mangano et al., sufficient data have not been available for an analysis of the risks and benefits of aprotinin. Furthermore, data-driven marketing efforts are under way to expand the indications for this drug. There is evidence that aprotinin modulates the systemic inflammatory response associated with cardiac surgery.³ This new application of aprotinin may require doses higher than those used for its primary indication — the reduction of bleeding and, hence, of required blood transfusion.^{4,5} The possibility of the use of higher doses has raised concern about increased toxicity. Accordingly, until the safety of higher doses is fully explored in a prospective study, the expansion of indications for aprotinin may be premature.

These concerns about the use of aprotinin can be addressed only by the analysis of data obtained from clinical practice and from well-designed clinical trials. Mangano et al. show the value of entities, such as the Multicenter Study of Perioperative Ischemia Research Group, that explore adverse outcomes in post-approval, or phase 4, studies. As pointed out by the authors, although this observational study was not a randomized trial, the incorporation of a large number of patients gives it credibility. In addition, the authors' conduct of an observational study implies an interesting point. When a clinical study is conducted long after a new drug has been approved and introduced into practice, established clinical practice (whether data-driven or not) makes stepping back to perform even an important clinical trial difficult — and makes observational studies a necessary alternative. It would be ideal, therefore, for phase 4 studies to be conducted as soon as possible after a drug has been introduced into clinical practice.

Clinical trials conducted by drug companies are designed to meet Food and Drug Administration (FDA) requirements for safety and efficacy. Under the current regulations, it is understandable that the indications tested in clinical trials are selected to achieve approval expeditiously and to balance patient care, the regulatory process, and business considerations. Although some exclusion criteria in clinical trials are used to ensure patient safety, such criteria decrease

the number of adverse events that might interfere with regulatory approval. Regulatory requirements and the desire to ensure approval often dominate the design of clinical trials. As a result, current phase 3 trials sometimes do not reliably gather information that is clinically useful for the safe expansion of indications, particularly for high-risk patients.

The study of aprotinin by Mangano et al. stands as an example of the importance of phase 4 clinical trials. Although the FDA can mandate the post-approval gathering of data, vendors are given the task of designing the subsequent clinical trials. Thus, the design of clinical trials may still be subject to business considerations. This conflict of interest creates a disincentive to fully explore the safety of a drug in various patient populations. Clinical-investigation groups such as the Multicenter Study of Perioperative Ischemia Research Group, which is able to recruit a large number of patients from excellent clinical centers, may offer the pharmaceutical industry a faster and more economical means of gathering phase 4 data. From the standpoint of patient safety, such research entities can explore new indications and dosing regimens in various patient populations and in a setting relatively free of conflicts of interest. In addition, input from academic medical centers may increase the likelihood of broader applications not originally considered by drug companies in the design of clinical trials.

Phase 4 clinical trials should be required before the indications for pharmaceutical agents are expanded, particularly when increased doses are required or administration in high-risk patients is proposed. Phase 3 studies may suggest that in certain settings, adverse events may occur in some patients, although the incidence in these trials may have been too low to allow full characterization of the events or exclusion criteria may have masked other important issues. Independent clinical research may be ideal for informing decisions to expand indications for pharmaceutical agents, for appropriate patient populations, or for dosing regimens to include previously unapproved doses.

The role of independent clinical research in phase 4 testing should be encouraged and supported by the FDA. The application of FDA data-quality practices in such studies would preclude criticisms of the data analysis, such as the lack of source documentation and the lack of on-site

review of the accuracy of data entry in the study by Mangano et al. Too many pharmacologic agents have entered into clinical practice for which considerable and potentially life-threatening outcomes were recognized only after a large number of patients had been treated. The recent example of cyclooxygenase-2 inhibitors is a high-profile case in point. Recognition of drug-induced toxic effects in certain patient populations or with increased dosing regimens must be reflected in clinical practice as early as possible in order to optimize patient safety.

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