Under the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) is charged with the approval of all new medical devices. The need to expeditiously approve new medical devices for the benefit of the public must be weighed against the need for deliberate and complete review of data to ensure that cardiovascular devices are both safe and effective.

These goals of speed and safety are at times in conflict and, some think, mutually exclusive. It is unrealistic to expect a device to be 100% safe. The debate among the FDA, manufacturers of cardiovascular devices, medical scientists, the public, and, perhaps most important, the legal community centers on what tolerance of uncertainty regarding safety will be accepted. Recent highly visible failures of interventional cardiology and heart valve devices have heightened the awareness of the difficulty faced by the FDA.

The FDA uses medical advisory panels composed of medical experts to review the data submitted by manufacturers of devices and to make recommendations regarding device approval based on these data. The quality of the data has varied widely and has stimulated the FDA, advisory panel members, and industry to find a way to improve the methods of testing devices, both to speed the approval process and to better evaluate the safety of devices. To this end, the FDA held a symposium in June 1993 to address these issues. Attending this meeting were representatives from industry, the medical community, the public, and the government. New guidelines on interventional cardiology devices, heart valves, and vascular grafts were developed by the FDA as a response to the concerns expressed at this symposium. The purpose of these documents is to guide the manufacturer in performing bench, animal, and clinical studies that will provide data to prove safety and effectiveness and ultimately lead to device approval.

Interventional Cardiology Devices

The recently promulgated draft “Guidance Document for the Submission of Research and Marketing Applications for Interventional Cardiology Devices” by the Office of Device Evaluation of the Food and Drug Agency has much to recommend it. Foremost is the stated preference that investigational device exemption (IDE) applications and subsequent premarket approval (PMA) applications use randomized controlled trials as the most reliable means of acquiring valid scientific evidence that a new device is safe and effective. The specific devices covered by the document are angioplasty catheters, atherectomy catheters, lasers, and intravascular stents. The document could also serve as a primer on “understanding the scientific method” because of the content, clarity, and conciseness of the seven pages devoted to clinical study requirements.

Also underscored in this “how-to” manuscript is proper patient screening and recruitment procedures so that patients are enrolled in a manner that eliminates selection bias. Protocols are expected to detail the procedure by which consecutive patients meeting the inclusion criteria are selected for possible enrollment. The aim is to identify the denominator that includes all qualifying patients who may have declined enrollment in the study or perhaps were not offered a chance for enrollment by the investigator. Also integral to the clinical study design are the clarity, precision, and accuracy of standard definitions of success, failure, and complications that must fit the goals of the trial. It is imperative that they be established before initiating the study and be used, without change, during patient enrollment and data analysis. Use of a separate data and safety monitoring committee is considered essential, and the establishment of an end point monitoring committee is strongly recommended. The increasing use of multiple or combined end points imposes a serious burden on such a committee, and this should be considered in constituting the committee membership. Clearly, this committee should be independent of the study investigators and industry representatives and should become, when possible, blind to patients’ treatment assignment.

This move on the part of the FDA for more rigorous trial design and study of transcatheter technologies is to be applauded, not cursed. We hope it will be embraced by the serious-minded, seasoned investigators who have the energy and vision to champion the use of nonsurgical techniques to accomplish successful myocardial revascularization. This brand of interventionalist has already demonstrated a commitment to using a randomized study design to minimize the introduction of the many biases that can so easily infiltrate the study of an interventional device. First, because the outcome of the disease under study is influenced by the baseline variables of the study population itself, it is imperative that the proposed treatment (device) be administered.
independent of patient characteristics. Randomization ensures that all known and unknown patient variables that could influence outcome are equally distributed between the study and control groups. Second, there are strong market forces created by the vested interests of the inventor, sponsor, and potential trialist, who often must invest substantially to purchase the device before trial participation, that must be recognized. These biform forces, plus the basic allure of new technologies, tend to create an unhealthy exuberance on the part of the trialist/investigator/interventionist. Objectivity in patient selection is rightly questioned and mandates that a randomization process be followed. Third, the practice of using new devices as a marketing strategy for patient referrals to a particular institution or the use of a specified “product-line” by an individual operator creates a climate of exclusivity that seriously constrains broad interchange and open investigation. It thus seems warranted that a new rigor be introduced to the design and conduct of clinical trials that will provide data for IDE and PMA applications. Although randomization may be the best method for clinical design, randomization must also be consistent with the ethical principles for protecting the subjects’ rights, safety, and welfare. Similarly, there will be new devices, technologies, or therapeutic strategies that cannot be tested against a suitable alternative therapy, and in these instances, alternate study designs will be accepted as long as they are rigorously conducted and eventually demonstrate the safety and efficacy of the device in question.

Replacement Heart Valves

There has been continuing debate concerning whether heart valves need randomized concurrent clinical controls. The surgical community has diverse opinions regarding the need for such controls. The new guidance document does not require controls with the rationale that the very low incidence of valve-related complications would require thousands of patients to detect differences. What the new document does require is far more extensive in vitro testing for fatigue and other structural characteristics. Advances in the sophistication of laboratory analysis make structural failure in implanted devices a remote concern.

Clinical trials would be used to compare the experimental valve with objective performance criteria developed by a comprehensive review of 30 years of data. As with all devices, structural failures will be required to be reported after the device is approved.

Vascular Graft Protheses

The vascular guidelines are less successful in providing a template experimental protocol for the manufacturer. This is due to the broadness of a set of guidelines that attempts to outline a protocol that would be applicable for all types of vascular grafts, from thoracic aortic replacements to coronary artery grafts. Limited animal studies and only 1 year of follow-up are required of prostheses. For example, objective assessment of the patency of coronary replacement grafts is required at 6 months and 1 year by either arteriography, echocardiography, or radioisotope imaging. One questions whether the safety or efficacy of a coronary graft can be determined by this protocol. Although the FDA has made a welcome attempt at template protocols, further refinement will be necessary.

References


KEY WORDS • regulation • Editorials
Cardiovascular devices and the Food and Drug Administration.
T J Ryan and J A Swain

Circulation. 1994;89:1903-1904
doi: 10.1161/01.CIR.89.4.1903

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/89/4/1903.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/