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REVIEW TOPIC OF THE WEEK

Overcoming the Challenges of Conducting Early Feasibility Studies of Medical Devices in the United States

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ABSTRACT

Initial clinical studies of new medical technologies involve a complex balance of research participant benefits versus risks and costs of uncertainty when novel concepts are tested. The Food and Drug Administration Center for Devices and Radiological Health has recently introduced the Early Feasibility Study (EFS) Program for facilitating the conduct of these studies under the Investigational Device Exemption regulations. However, a systematic approach is needed to successfully implement this program while affording appropriate preservation of the rights and interests of patients. For this to succeed, a holistic reform of the clinical studies ecosystem for performing early-stage clinical research in the United States is necessary. The authors review the current landscape of the U.S. EFS and make recommendations for developing an efficient EFS process to meet the goal of improving access to early-stage, potentially beneficial medical devices in the United States. (J Am Coll Cardiol 2016;68:1908–15) © 2016 by the American College of Cardiology Foundation. All rights reserved.

Clinical evaluations of innovative medical technologies are designed to optimize care while offering opportunities for both research participants and society alike. An optimal approach takes into consideration the risk-benefit ratio needed for the efficient generation of robust evidence, while determining which technologies will evolve to address unmet, important clinical needs. There has been a migration of clinical studies for medical devices out of the United States: in 2004, 87% of clinical studies for medical technology products listed on ClinicalTrials.gov were conducted in the United States, whereas by 2009, that number dropped to 45% (1). This trend has stimulated an examination of the U.S. system of clinical trials, because the integration of research into practice is a critical component of the continuum of advancement of medical care and can provide early availability of potentially beneficial devices for U.S. patients with timely regulatory approval.

The Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) has recognized that the migration of clinical studies can be partly explained by the more comprehensive regulatory requirements for conducting U.S. clinical

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studies (2). Historically in the United States, justification to initiate an early device clinical study has required extensive nonclinical testing to provide a sound scientific basis that exposing patients to the device is appropriate; however, it has been recognized that this amount of testing may have impeded effective device development, given the likelihood of early device design to change and the lack of predictability of the nonclinical testing on clinical outcomes. In addition, the ability to incorporate additional patient protection measures in early studies to mitigate potential risks has been missing.

Assessment of the appropriate regulatory requirements includes consideration of the fact that there are important differences between studying devices and studying drugs. In clinical trials of drugs, the structure of the drug to be studied is finalized at the start of the trial and does not change. In contrast to evaluation of new drugs, in device development, there is an expectation of an iterative process in which a prototype is modified, often many times, on the basis of information obtained in a relatively small number of initial research participants in early feasibility studies, and then the finalized design is assessed in a larger, pivotal study of safety and effectiveness. Recognizing the distinctive regulatory challenges associated with early device clinical studies, FDA CDRH introduced the Early Feasibility Study (EFS) Program (3), intended to transform the system and facilitate access to new medical device technology.

However, FDA guidance is not sufficient. For successful implementation of the EFS program, a holistic approach is required, in which all stakeholders in the clinical trial enterprise work collaboratively to optimize the speed, safety, data quality, and financial costs and reimbursement of U.S. medical device development, and to optimize evidence generation to determine their clinical safety and effectiveness. This new paradigm will require compromise and commitment by a consortium of all stakeholders (**Table 1**) to view EFS projects differently, accepting that changes to current clinical practice may be needed to fulfill the essential goal of providing the best available, safe, and effective technology to U.S. patients earlier than previously possible.

TABLE 1 Stakeholders in EFS Projects

Patients	IRBs
Investigators	Clinical study sites
Sponsors	Payers
FDA	Public and private funders

EFS = early feasibility study; FDA = Food and Drug Administration; IRB = institutional review board.

An illustration of the inadequacies of the current system is provided by the U.S. EFS transcatheter mitral valve replacement (TMVR) initial experience. Severe mitral regurgitation (MR) is a cause of heart failure in a large number of patients, many of whom are at high or prohibitive risk for open surgical mitral valve repair or replacement. Although 1 device is FDA-approved for catheter-based treatment of primary severe MR (4), additional approaches are required, especially for secondary severe MR. Several platforms have been developed, and TMVR EFS Investigational Device Exemption (IDE) applications have been approved for at least 5 devices. Although there has been great enthusiasm for these EFS studies in the United States, significant challenges have already been encountered that have delayed study initiation and execution: lengthy institutional review board (IRB) review, inadequate site administrative infrastructure, insufficient access to the requisite patient population, and difficulties in contract negotiations and reimbursement. This paper suggests approaches to improving the U.S. EFS ecosystem on the basis of the authors' personal experience with the EFS Program.

ABBREVIATIONS AND ACRONYMS

CDRH = Center for Devices and Radiological Health

CMS = Centers for Medicare & Medicaid Services

EFS = early feasibility study

FDA = Food and Drug Administration

IDE = Investigational Device Exemption

IRB = Institutional Review Board

MR = mitral regurgitation

TMVR = transcatheter mitral valve replacement

BACKGROUND ON EFS

Studies of significant risk devices, such as heart valves, require FDA approval through an IDE application and site IRB approval before initiating participant enrollment (5,6). An EFS IDE involves a limited clinical investigation of a device that is either early in development or being evaluated for a novel intended use; it may be used to assess the device design concept with respect to initial clinical safety and device functionality in a small number of research participants when this information cannot practically be provided through nonclinical assessments. These pilot studies may inform subsequent device modifications and future clinical study designs (3) (**Central Illustration**).

EFS STAKEHOLDERS

Strengthening the environment for device innovation and helping patients gain earlier access to beneficial medical devices begins with acknowledging the unique benefits and motivations among the different stakeholders (**Table 2**).

Participation may provide the following benefits:

1. *Patients* may gain earlier access to a device that may improve their own health or advance the standard of care for others, without the need for