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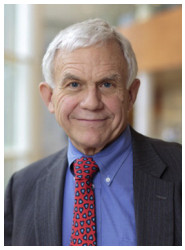

Clinical Perspective—Early Feasibility Device Medical Studies in the United States

Time for More Than Regulatory Reform

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Everyone complains about the weather but no one does anything about it. The problem of outsourcing of early development and evaluation of medical devices has been like the weather; everyone complains but little has been done. What follows is a call to action to engage all of us to expand beyond the FDA's recent initiative, the Early Feasibility Study Program, to align all the players to finally do something."

—Spencer B. King III, MD

Concerns have been raised in the United States about the out-migration of new medical device development and evaluation and its important impact on the timeliness of patient access (1). These have been raised by multiple stakeholders—patients, clinicians, professional societies, medical device industry, and regulatory agencies—alike. A relevant recent example is transcatheter aortic valve replacement (TAVR); the United States was the 43rd country to approve what is now considered to be transformational technology (2).

Whereas diligent clinical evaluation of new innovative technology is critical to determine the potential benefits while protecting individuals and the public from the risks of new devices, efficient processes for optimizing and streamlining regulatory pathways are needed so that new, safe, and effective treatment strategies can be developed for unmet clinical needs. Each stakeholder group needs to be fully engaged, and all groups will need to make compromises and adjustments in generating the medical evidence required to allow access for U.S. patients to these potentially lifesaving safe and effective devices in a high-quality efficient manner.

Regulatory requirements for devices differ from those for drugs because the methods of evaluation must take into account their unique features. In the latter, the drug under consideration is fixed and then tested in increasingly larger patient numbers at varying doses to assess benefits and risks for intended uses. In contrast, devices are developed through an iterative process wherein a prototype is modified and pivotal study endpoints are selected on the basis of the results of early studies as the potential of the device for favorable effects in clinical problems becomes better clarified. The U.S. Food and Drug Administration (FDA) responded to the distinctive challenges of early device U.S. clinical studies with a program intended to transform the system for early device development—the Early Feasibility Study (EFS) Program—which began with the publication of the EFS Guidance document in 2013 (3).

This program recognizes that early device development is an iterative process and that appropriate

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approval of an EFS Investigational Device Exemption protocol may be on the basis of less rigorous nonclinical data than is necessary for final device approval. It takes into account the unmet clinical needs to be addressed and uses enhanced patient protection measures to mitigate unknown clinical risks. Its primary goals are to foster robust early evidence generation for continued efficient device development and timely patient access to new beneficial technologies.

During the EFS process, while evaluating another innovative medical device for transcatheter mitral valve replacement, it became apparent that more than regulatory reform of the clinical trial infrastructure for performing early stage clinical research in the United States is necessary for successful and efficient early device development. In this instance, there were delays implementing EFS at clinical research sites due to the unique issues associated with these studies; these included institutional review board (IRB) processes and lack of consensus about appropriate contractual requirements at the clinical sites involved, resulting in delays in trial performance.

Successful implementation of the benefits of the EFS Program requires a holistic approach including active engagement and the acceptance of reasonable trade-offs by all stakeholder groups. The U.S. clinical studies ecosystem is complex; transformation will require at a minimum a consideration of patient, physician, hospital, legal, IRB regulatory agency, and sponsor involvement. For example, IRB have been challenged to accept the uncertainties of EFS protocols due to the difficulty in anticipating risks, particularly for implantable devices that may cause serious harm. However, considering the benefit-risk balance offered by EFS, robust mitigation strategies and patient protections can be applied, particularly if relevant institutional human research protection programs are involved in a broader network of clinical trial sites that adheres to common standards for quality and performance. EFS could also provide IRB members with valuable early exposure to new technologies and increase the efficiency of subsequent IRB evaluations of pivotal studies. Other clinical study ecosystem participants will need to accept a greater degree of risk, greater accountability, and expend additional time and resources. Risks include the uncertainty around the potential adverse effects and probability of benefit for the research participants themselves and for those responsible for patient care and study oversight. Additionally, there are the risks of working within a relatively novel U.S. EFS clinical study system, including not only the risk of clinical harm and its consequences for patients, clinicians, and health systems, but also risks related to returns on investment of time and money including expenditures for study initiation, participation, conduct, and oversight. However, the return on investment for all participants and the U.S. health care system as a whole can be large.

A concerted effort by all ecosystem participants to make critical improvements is needed. EFS clinical site selection criteria to optimize patient recruitment and promulgation of successful timely trial execution must be developed and implemented and site leadership should commit to meet these criteria. Allocating resources, the FDA and clinical experts should provide support and a forum to exchange the best ideas to optimize protocols with IRB's. IRB's should commit to timely protocol reviews and device regulations, and federal law should be modified to allow for routine use of central IRB's, recognizing that protocol review does not change an institution's responsibility to oversee human subjects' protection at a local level as studies are conducted. Clinical sites, industry, and funders will need to develop an approach to managing liability risk approaches through appropriate and standardized contractual agreements. Centers for Medicare and Medicaid Services and other payers should work together with other members of the EFS system and especially the FDA to develop an approach to determining how EFS can be appropriately reimbursed (4,5). Patient groups should provide input on study protocols and informed consent forms to encourage development and investment in clinically meaningful device innovation by highlighting the needs associated with their specific clinical conditions and advocating for appropriate protocols and devices to meet these demands.

The EFS initiative by the FDA is an important first step to allow patient access to early stage medical devices and ultimately timely patient access to those demonstrated to be safe and effective. However, on the basis of initial experiences with this program, a holistic rather than solely regulatory approach to modify the existing clinical trial infrastructure is necessary. Unless these modifications are made, we—society, and particularly patients—will not be able to fully realize the potential of this program.

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