Mitral Valve Academic Research Consortium consensus report: the U.S. Food and Drug Administration perspective*

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This editorial refers to ‘Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles’†, by G.W. Stone et al., on page 1851 and ‘Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions’‡, by G.W. Stone et al., on page 1878.

The U.S. Food and Drug Administration (FDA) is responsible for protecting and promoting the public health of U.S. citizens. In keeping with this mission, the FDA’s Center for Devices and Radiological Health (CDRH) is tasked with ensuring the safety, effectiveness, and quality of medical devices; fostering innovation; and providing the public with accurate scientific information about the products they oversee throughout the total product life cycle. To help fulfill its mission, the CDRH has an ongoing interest in promoting the quality and efficiency of clinical trials. Clinical trials that produce high levels of valid scientific evidence to meet the regulatory approval threshold of reasonable assurance of safety and effectiveness are dependent on excellent trial design and execution. To this end, clearly defined clinical events and meaningful study outcome endpoints are essential elements for trials submitted for regulatory review. Collaborative efforts among multiple stakeholders to reach agreement on trial design elements and standardized definitions for meaningful clinical endpoints are especially important when unmet medical needs call for the timely development of safe and effective medical devices. The FDA supports these cooperative efforts as a tool to help achieve shared goals of providing innovative medical device solutions to critical public health challenges.

Prior multidisciplinary collaboration under the umbrella of the Valve Academic Research Consortium (VARC) produced consensus regarding standardized definitions for adverse events and clinically meaningful single and composite endpoints (VARC1 and VARC 2) for device-, procedure-, and patient-related safety and effectiveness measures for transcatheter aortic valve replacement device trials. Following a similar model, the Mitral Working Group of the Valve Academic Research Consortium (MVARC) brought together an international multidisciplinary group of leading academic research organizations, physician-scientists, regulators, and industry representatives to provide recommendations for clinical study designs and endpoint definitions for evaluating new transcatheter mitral valve replacement and repair devices. The resulting 2-part document (1,2) provides an important summary of the collective recommendations of MVARC, and from a regulatory perspective, offers important suggestions on the design and endpoints of clinical trials intended to support pre-market approval applications. Appropriate adoption of the common definitional framework and trial design recommendations put forward in these documents will help avoid future problems with trial design that can adversely affect the ability to analyse data. Failure to identify and classify appropriate study populations or failure to define and use suitable individual or composite endpoints that are adequate for providing reasonable assurance of safety or effectiveness can be obstacles to device approval. The MVARC documents aim to address these issues proactively.

Appropriate use of MVARC recommendations regarding clinical trial design and definitions for single and composite endpoints can facilitate the FDA’s review of investigational device exemption submissions to permit initiation of worthwhile clinical trials in the United States. Further, uniform event definitions and meaningful study endpoints can improve the quality of pre-market approval submissions to the FDA and enhance the efficiency of data review and regulatory decision-making.
In contrast to aortic stenosis, the pathophysiology of mitral regurgitation (MR) is complex and involves a wide spectrum of valvular and ventricular pathologies. The design of medical devices aimed at treating MR will have different characteristics and goals on the basis of the underlying disease state. Importantly, MVARC recognized the complexity of MR, and the publication of their recommendations is particularly useful during the early development stage of transcatheter mitral devices. Specifically, the MVARC initiative coincides in timing with the early clinical evaluation of several transcatheter mitral repair and replacement devices in the United States and abroad. The participation of U.S. sites in these crucial early trials is an important result of 1 of CDRH’s strategic priorities—promoting early feasibility studies in the United States. The recommendations by MVARC will be tested and may be refined during these early studies, and it is hoped that U.S. early feasibility studies will facilitate an efficient transition to future pivotal clinical trials and, ultimately, earlier access for U.S. patients to novel technologies. Harmonized endpoint definitions incorporated into pre- and post-market data collections utilizing national or international registries can further increase the efficiency in conducting clinical studies. Success in these areas will help diminish the current time lag that exists in the availability of some beneficial medical devices in the United States compared with other regions of the world, an increasingly important concern among U.S. patients and physicians.

We believe it is critical to utilize our regulatory authority and understanding of the products we oversee in establishing collaborative working relationships with our partners in the federal government and external constituencies to advance innovative approaches to benefit public health. We continue to encourage sponsors to contact the Agency early in device development to facilitate efficient, timely initiation of clinical trials intended to support FDA approval. Although a common set of definitions and endpoints is very helpful, specific trial design elements may depend on the particular device and patient population being studied. FDA approval to initiate a clinical study of an investigational device also depends on meeting the requirements for nonclinical testing that are relevant to the anatomically and hemodynamically challenging mitral environment. Therefore, it is extremely important that sponsors understand the FDA’s nonclinical testing expectations as early as possible to make efficient use of time and resources. High-quality study execution, integrity, and validity are critically important for clinical trials submitted to the FDA; efforts to ensure adequate subject follow-up, minimize missing data, limit bias, adjudicate events independently, and the use of a pre-specified statistical analysis plan (with adequate control of type I error) are important considerations in our regulatory review. It is our hope that publication of the MVARC document will encourage sponsors and investigators to make use of early interaction with the Agency. For this field to mature at an optimal pace in the United States, it is essential that the FDA, sponsors, and investigators continue to collaborate closely to develop high-quality nonclinical and clinical data that ultimately result in beneficial devices for patients.

FDA also applauds the “global” approach adopted by MVARC, in terms of both geography and expertise (international representation of surgeons, interventional cardiologists, clinical cardiologists, clinical trialists, other allied specialists, and industry), which we believe was instrumental to the success of this effort. Such a process allowed for an open and balanced discussion of complex issues. Finally, the consensus report represents an important step in a dynamic process, and the Agency looks forward to continued involvement with MVARC as the technology and clinical application of transcatheter mitral replacement and repair devices evolve.

Conflict of interest: none declared.

References