Abstract—The incorporation of complex medical device technologies into clinical practice is governed by critical oversight of the US Food and Drug Administration. This regulatory process requires a judicious balance between assuring safety and efficacy, while providing efficient review to facilitate access to innovative therapies. Recent contrasting views of the regulatory process have emphasized the difficulties in obtaining an optimal balance. Mechanical circulatory support...
Background and Purpose

The incorporation of complex medical device technologies into clinical practice is governed by critical oversight of the US Food and Drug Administration (FDA). This regulatory process requires a judicious balance between assuring safety and efficacy, while providing efficient review to facilitate patient access to innovative therapies. The regulatory approval process in the United States is complex owing to the increasing technical sophistication of devices and the dynamic nature of the medical device industry. Increasing scrutiny has been placed on the regulatory process because of concerns about introduction of unsafe technologies into the medical community, while the medical device industry and some clinicians have perceived the process of obtaining regulatory approval of new devices as inefficient and lengthy.1–5

Recently, physicians representing The Society of Thoracic Surgeons, American Heart Association, American Association for Thoracic Surgery, Heart Failure Society of America, American College of Cardiology Foundation, and the International Society for Heart and Lung Transplantation, and representatives from the FDA, National Institutes of Health, National Heart, Lung, and Blood Institute, Centers for Medicare and Medicaid Services (CMS), Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS), medical insurance providers, and industry partners gathered to discuss relevant issues regarding the current regulatory environment assessing ventricular assist device therapy. The goal of the meeting was to explore innovative ways to foster the introduction of technologically advanced, safe, and effective ventricular assist devices. The following summary reflects opinions and conclusions endorsed by The Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, Heart Failure Society of America, International Society for Heart and Lung Transplantation, and the Interagency Registry of Mechanically Assisted Circulatory Support. (Circ Heart Fail. 2013;6:145–150.)

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has evolved to become an important therapy for patients with advanced heart failure with the advent of more durable, implantable ventricular assist devices. The regulatory oversight of these new technologies has been difficult owing to the complexities of these devices, associated adverse event profile, and severity of illness of the intended patient population. Maintaining a regulatory environment to foster efficient introduction of safe and effective technologies is critical to the success of VAD therapy and important to improving the health of patients with advanced heart failure. The goal of the meeting was to explore innovative ways to foster the introduction of technologically advanced, safe, and effective ventricular assist devices. The following summary reflects opinions and conclusions endorsed by The Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, Heart Failure Society of America, International Society for Heart and Lung Transplantation, and the Interagency Registry of Mechanically Assisted Circulatory Support. (Circ Heart Fail. 2013;6:145–150.)

Innovative Clinical Trial Designs

Randomized controlled trials are recognized as the gold standard for evaluating the safety and efficacy of new therapeutics. With respect to the clinical evaluation of VAD therapy, a randomized controlled trial to test superiority of one device over another is not feasible owing to the impractical size and costs associated with sample sizes to detect small differences in comparable devices with respect to efficacy and safety. Noninferiority trial designs or use of concurrent observational controls from registries such as INTERMACS may permit development of unique trials designs that would facilitate practical yet rigorous scientific evaluation of devices.50 However, the use of registries has significant limitations that must be recognized, particularly in the evaluation of new patient populations or novel devices. Endpoints in future trial designs...
should emphasize the need for improved evaluation of functional and quality of life variables.

Summary Opinion

1. The use of registry data should be further developed to provide alternative trial design options for the use of a contemporary comparator for VAD trials. The challenges associated with this approach were identified, and consensus was reached that more work is needed to develop and refine methodologies to support this new direction.

2. Presubmission meetings, early in the process, with all stakeholders including FDA, CMS, industry, and clinicians should occur to optimize trial design.

3. Registry data are not an acceptable comparator for studies of novel technology or of novel patient populations that are substantially different from the current evidence-based therapies.

4. Historical controls or performance measures are currently inadequate comparators for evaluation of devices for destination therapy (DT) and inadequate to study new device indications.

5. INTERMACS will be integral to device evaluation. The process of incorporating INTERMACS into the regulatory process of device evaluation needs to mature. Ensuring complete and robust data capture is an important ongoing INTERMACS imperative. Collaborative input from the FDA, CMS, industry, and clinicians is necessary for this process to be successful.

6. Consensus needs to be developed regarding the most appropriate functional endpoint for VAD trials. Although VO2 max has been validated as an endpoint in heart failure patients with cardiac resynchronization, it has not been validated in VAD patients. Further research is needed to determine whether functional endpoint data (6-minute walk, quality of life) can be collected in a nonclinical trial setting (eg, INTERMACS) at a level of rigor sufficient to minimize bias and to allow robust comparisons to investigational devices.

Development of an Encompassing Indication for Device Therapy

The implant strategies and indications for the use of durable MCS devices for the treatment of advanced heart failure currently include bridge to transplantation and DT. These treatment paradigms for using VADs have paralleled the historical development of this therapy. The clinical relevance of distinguishing between MCS as a bridge to transplant, bridge to candidacy, bridge to recovery, or DT has been debated in the literature. Some view these classifications as clinically artificial, as patients may transition from one designation to another depending on the resolution or occurrence of comorbid conditions or patient choice. It has been proposed that MCS devices should be evaluated, approved, and reimbursed according to “short-term” (eg, devices not permitting patient discharge) and “long-term” (eg, devices that are implantable and permit patient discharge with untethered mobility) MCS indications. A single indication of long-term MCS may shorten development time and cost for new devices, requiring only one trial to investigate a single indication rather than committing industry to the complexities of multiple trials to establish multiple indications for a single device.

Summary Opinion

1. The current indications of bridge to transplant and DT have limitations and create disparities in device access for patients.

2. A single indication of long-term support for VAD therapy would need to facilitate both device evaluation and improve access of device therapy to patients.

3. Before a transition to a single long-term MCS indication could be adopted, all stakeholders (FDA, industry, academic investigators, and payors) must have open dialogue and examine detailed scenarios for how such a trial would be operationalized. Collaboration with regulatory agencies earlier in the process of device assessment may improve feedback and reduce inefficiencies in the regulatory process.

4. The FDA and CMS should work together throughout the regulatory process to ensure that investigational device exemption–approved studies leading to premarket approvals yield both FDA approval and CMS coverage, to avoid lag times between marketing approval and reimbursement. This may require CMS to change its reimbursement categories before this change can occur.

Assessing International Standards of Regulatory Evaluation

Exporting operational components of clinical research is not unique to VAD clinical trials. First, the processes for conducting a cardiovascular device trial in the European Union are generally less burdensome than in the United States. Active, randomized controls are not always required, which allows smaller trials to be conducted, and clinical research costs are generally lower. The Conformité Europénne (CE mark) that is required for marketing in the European Union can be obtained more quickly, with lower costs and less complexity compared to in the United States. Currently, an optimal global regulatory environment for assessment of MCS devices is absent. In the United States, some view the regulatory environment as restrictive resulting in disincentives to develop innovative technology, whereas in the European Union, the regulatory environment is viewed as less strict and inadequate to completely evaluate safety and efficacy before marketing. Each system has its strengths and weaknesses.

One approach to address this barrier and bring feasibility or first-in-human studies back to the United States is to incorporate early safety assessments into the pivotal trial. With this approach, early trial enrollment would be limited to a small number of patients at select implant centers. An interim safety analysis would be required before enrollment is opened to a larger patient population at more centers. Harmonization of standards across countries is an important issue that is currently lacking, but needs to be addressed for data exchange to be meaningful.
Summary Opinion

1. The use of international data to support US clinical trials and regulatory pathways requires further exploration. Utilization of more trial data from international sources would require harmonization of definitions of adverse events and require similar levels of adjudication of adverse events with similar oversight as performed in the United States. Novel approaches that allow inclusion of patients data from outside the United States are warranted.

2. While regulatory oversight is necessary to ensure marketed devices are safe and effective, strategies to incentivize preclinical development to remain (or return) to the United States are needed.

3. Areas where preclinical and pilot studies could be shortened or combined with pivotal studies should be explored. Preclinical study designs are needed that satisfy both the FDA’s regulatory demands as well as allow for a broader acceptance of performance criteria, but the optimal design is yet to be determined.

Preclinical Device Evaluation

Historically, problems with MCS device durability have been detected, in part, through clinical testing and surveillance as the technology and methodology to perform more robust preclinical testing is not available. Several standards now form the mandatory foundation of preclinical development programs. These standards direct developers to focus on a system’s most critical potential faults and to plan for appropriate mitigations should such failures be detected during testing. The development of more robust preclinical reliability standards would be helpful to establish the clinical readiness of new devices, and to accelerate innovation. A challenge that remains to be addressed is a manufacturer’s hesitancy to modify devices studied in ongoing trials due to regulatory concerns that trials would have to be repeated if the device is substantially modified.

Biological Reliability and Human Factor Concerns

An ongoing challenge facing preclinical testing is the assessment of MCS device biological reliability and pertains to the device–patient interface. Animal models to date have been inadequate to answer these questions, and different responses across species have been observed that often do not comprehensively reflect the human response.

Peripheral Failures

The reliability of continuous flow pumps has markedly reduced concerns regarding pump failure, but peripheral component failures continue to be an area of focus for preclinical evaluations. A major limitation with preclinical MCS device reliability testing is the inability to comprehensively reproduce all clinical failure modes of peripheral components.

Summary Opinion

1. Accelerated testing methodology to identify specific failure modes before clinical introduction of devices is necessary to improve the efficiency of the regulatory approval process.

2. Novel testing methods to assess the biological reliability of devices before the clinical introduction of device should be developed. Enhancement of reliability through the development of novel biomaterials and implantable components is an area of needed research.

3. Development of a robust preclinical reliability standard would be helpful to establish the clinical readiness of new devices, and to accelerate innovation. The impact in terms of cost and added preclinical testing to increase component reliability is not known. Future devices should report preclinical testing using similar if not identical testing methods to allow better comparison for safety evaluation before first-in-human studies.

4. Committing to standardized preclinical testing coupled with improved testing for biological compatibility, may reduce the time required for MCS device preclinical testing and may result in more devices being available for future trials.

Regulatory Evaluation in the Pediatric Population

To date, two pediatric VADs have been approved in the United States under the humanitarian device exemption program. The humanitarian device exemption program facilitates development of devices when the intended population to treat is fewer than 4000 patients annually. Fostering device development for the pediatric population has been an important initiative by the National Heart, Lung, and Blood Institute and the medical community. The PumpKIN program initiative is a collaborative effort designed to evaluate new technologies for MCS therapy in the pediatric population and will evaluate four devices, including two advanced compact extra-corporeal systems and two VAD systems in pediatric patients with advanced heart failure. Pediatric MCS device development faces unique challenges, as well as challenges common to adult MCS. Mechanical circulator support with a durable VAD in the pediatric population is an immature area of both clinical practice and research characterized by incompletely understood issues that need to be addressed in future trial designs. The humanitarian device exemption process requires an assessment of probable benefit and risks associated with MCS devices. However, the risks of standard of care in pediatric patients who are critically ill with advanced circulatory failure have not been well characterized. Thus, it is difficult to place risks associated with MCS therapy into context of the risks of existing therapy. Further registry research is needed to describe the clinical features and outcomes in the pediatric population. The clinical and research community must define the expected “probable benefit” for MCS therapy in the pediatric population. Probable benefit may take the form of supporting a patient who would otherwise not survive to transplant, or providing long-term support in the form of DT.
Investigators and industry sponsors have an opportunity to enter into a dialogue with FDA regarding the ideal definition for probable benefit as studies are being designed.

It is recognized that the pediatric population poses numerous challenges to the application of MCS therapy. These challenges include the following: (1) the small numbers of the intended population to treat limiting clinical trial size, clinical management experience, and outcomes evaluation; (2) variable physical size of the intended population to treat ranging in age from days to 18 years, requiring the possible need for several devices to support a patient over the course of the patient’s lifetime; (3) unique anatomy due to physical size or presence of congenital heart disease that may require alternative pump configurations or alternative implantation techniques; (4) lack of experimental or animal models of congenital heart disease to assist in the development of novel pump designs; (5) concerns for the diagnosis, assessment, and impact of adverse events; and (6) variable cognitive development, especially concerning self-care and understanding of the device. That is particularly relevant to the occurrence of stroke for which neurologic assessment in pediatric patients is difficult, the experience with anticoagulation therapy in the pediatric population is limited, and long-term data on the impact on developmental delays are unknown.

Summary Opinion

1. Expected probable benefit for device therapy in the pediatric population needs to be defined.
2. Focus should be placed on areas in which pediatric research can be applied to adult patients, as an incentive to innovation in the pediatric arena.
3. More research is needed on novel devices to meet the unique physiology needs of patients with congenital heart disease.
4. More data are needed to describe the clinical characteristics and outcomes of pediatric patients.
5. More experience with preventing and managing neurologic outcomes in pediatric patients is needed.

Summary

The regulatory assessment of MCS device technologies in the United States is complex owing to the sophistication of devices and quickly evolving nature of device development. The current regulatory evaluation of devices is lengthy owing to a number of critical factors including lack of consensus on trial designs, meaningful outcomes for trials, and statistical methodologies to assess outcomes, lack of available and robust data to serve as comparator, multiple device indications, lack of uniform preclinical testing standards, and differing regulatory and reimbursement requirements. All parties uniformly agreed that introduction of innovative methodologies to conduct the preclinical and clinical evaluation of MCS devices is necessary to foster an environment of device innovation and improve assessments of safety and efficacy and efficiency of the regulatory process in the United States. The challenge for the field will be to ensure that all stakeholders in the process benefit from changes to the regulatory procedures, with safety and efficacy being of paramount and fundamental importance in guiding the decision process. It is critical for experts in the field to be actively involved and to partner with the FDA in all aspects of MCS development including trial design, outcome assessments, data interpretation, and regulatory evaluation. Active involvement of CMS in this process is also critical for efficient introduction of devices into clinical practice. Professional societies may be uniquely positioned to provide a mechanism for bringing together a balanced group of experts (academic researchers and clinician leaders) who can engage with the FDA. The health burden of heart failure in the United States increases the urgency of the mandate for change.

References


Appendix

Author Relationships With Industry: Statement Regarding the Pre and Post Market Assessment of Durable, Implantable Ventricular Assist Devices in the United States: Executive Summary

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