Statement Regarding the Pre and Post Market Assessment of Durable, Implantable Ventricular Assist Devices in the United States

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

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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
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 The US House Energy and Commerce Subcommittee on Oversight and Investigations held a hearing on July 20, 2011, entitled “Medical Device Regulation: Impact on American Patients, Innovation, and Jobs,” and examined, in part, the migration of US device companies abroad to develop and evaluate innovative medical devices.6 On July 29, 2011, the Institute of Medicine released an FDA-commissioned report on the 510(k) clearance process and concluded that it was impossible for the 510(k) regulatory pathway to assure safety and effectiveness of medical devices.7 These contrasting views of the regulatory process emphasize the critical balance between ensuring safety and efficacy and permitting timely access of innovative devices to patients.

Mechanical circulatory support (MCS) has evolved to become an important therapy for patients who have advanced heart failure, with the advent of more durable, implantable ventricular assist devices (VAD).8 Innovative technological advances in durability and reductions in device size have fostered growing adoption of this therapy by physicians and patients.9 The regulatory oversight of these new technologies has been difficult owing to the complexities of MCS devices, associated adverse event profile, severity of illness of the intended patient population, heterogeneity of device designs, and varied implantation indications. 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.


Key Words: AHA Scientific Statements ■ heart-assist device ■ heart failure

Abbreviations and Acronyms

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<tr>
<th>Abbreviation</th>
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<tr>
<td>BTC</td>
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<td>BTT</td>
<td>bridge to transplant</td>
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<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
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<td>DT</td>
<td>destination therapy</td>
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<td>INTERMACS</td>
<td>Interagency Registry of Mechanically Assisted Circulatory Support</td>
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<td>mechanical circulatory support</td>
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<td>NHLBI</td>
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<td>PMA</td>
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exploring methods for preclinical MCS device evaluation; and (5) development and regulatory oversight of MCS devices in the pediatric population. In each area, critical questions were raised, and perspective was provided by panel members.

This paper summarizes the discussions that took place at this pivotal meeting. Consensus among the experts was reached for some issues, whereas other areas were identified where more data are needed to advance the field toward agreement. The overarching goal of both the meeting and this document is to serve as a platform to launch next steps toward achieving a collaborative effort focused on bringing safe and effective MCS therapies to appropriate patients in an efficient, consistent, and economically responsible manner.

Innovative Clinical Trial Designs

Are Active-Controlled Large Randomized Clinical Trials Necessary to Establish Long-Term Safety and Efficacy for Destination Therapy?

Randomized controlled trials are the gold standard for evaluating the safety and efficacy of new therapeutics. These trials allow objective comparison of a new therapy to the existing standard of care, or to placebo where a standard of care does not exist. In the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, subjects were randomly assigned to VAD therapy or to optimal medical management alone, which was the standard of care at the time for patients ineligible for heart transplantation (eg, destination therapy [DT]). In the REMATCH trial, VAD therapy improved survival and quality of life relative to optimal medical management. These findings raised the bar for the “standard of care” for future MCS randomized trials, such that a comparator VAD group would be required to achieve clinical equipoise, at least for trials enrolling subjects similar to those represented by the REMATCH study.

Using a VAD comparator, while clinically and ethically appropriate, introduces practical challenges in clinical trial design. Although the continuous flow device (HeartMate II) has recently been shown to be superior to the original pulsatile device (HeartMate XVE) utilized in the REMATCH study for DT evaluation, it is unlikely that new continuous flow devices will provide similar significant incremental advances in survival compared with existing devices. Instead, technology advances are more likely to result in improved adverse event profiles (eg, reduction in neurologic events) or other device-specific characteristic (eg, reduction in size, improvement in durability, or ease of implant technique). Trials designed to demonstrate superiority of one device will not be feasible because prohibitively large sample sizes would be required to demonstrate small efficacy differences, escalating costs and time required to conduct such clinical trials. Recognition of these challenges has led to the consideration of innovative trial designs that meet the regulatory standard of generating unbiased safety and efficacy data, while enabling trials to be conducted in a more expeditious manner.

A noninferiority design represents an alternative option when comparing a new device to an existing device. The sample size required to rule out important differences in outcome for a noninferiority trial design will depend upon the size of the selected noninferiority margin. Selection of a wide margin may bring the scientific validity of the results into question and such specifics should be discussed early during the development stage of the clinical trial design with appropriate regulatory experts. Approved and readily available technologies may also be difficult to control in a noninferiority design and may confound the interpretation of the results.

Historical controls or performance measures as the comparator have been utilized to assess VAD therapy for bridge-to-transplant (BTT) indication but not for DT. These trial design strategies address the issue of sample size, but create challenges with regard to data interpretation as a consequence of (1) temporal changes in standards of care and therapeutic advances that alter the natural history of a disease; (2) bias of increasing operator and patient management experience over time; and (3) difficulty matching baseline characteristics and risk of a historical control group with a contemporary patient cohort. Baseline risk has been established as an important determinant of outcome after VAD implantation, emphasizing the need to accurately match baseline characteristics and thus, limiting the use of historical controls or performance measures to assess new devices for DT. Further, historical controls do not exist for less severely ill populations with heart failure. As research initiatives move toward this patient population, randomized comparisons may be required to establish safety and efficacy.

The INTERMACS registry is a unique resource that has the potential to facilitate device evaluation and trial design in the United States. It is a national registry for patients who are receiving MCS therapy to treat advanced heart failure. This registry was devised as a joint effort of the NHLBI, CMS, FDA, clinicians, scientists, and industry representatives. The contemporary nature of data collection in the INTERMACS registry captures changes in practice standards and outcomes. Sophisticated statistical techniques can be used to create a comparable population that resembles the baseline risk of a study population. However, limitations in these statistical methods do exist that prevent complete assessment of baseline risk. The comparator group should have a similar severity of heart failure (as defined by INTERMACS profiles), comorbidities, and risk of right heart failure. These may be difficult to match retrospectively, as evidenced by the Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) trial experience. ADVANCE was the first study designed to compare a VAD, in a BTT population, to a control population derived from the INTERMACS study. Statistical methodology was utilized to control for baseline characteristics between the treatment group and the INTERMACS group. However, because of a large amount of missing data on one of the covariates, the validity of the propensity score analysis was called into question. Before the propensity score adjustment, significant differences were noted in the distribution of INTERMACS patient profiles, with more control group patients being in profiles 1 or 2 (eg, more advanced disease) and a greater proportion of treatment patients in profiles 3 or 4 to 7.

For INTERMACS to serve as an acceptable control for future trials, the data must be comprehensive, complete, and reliable. From its inception, several features of the INTERMACS registry have distinguished it from traditional registries in terms of scientific rigor, including consistent
adverse event definitions, auditing of high priority variables (eg, terminal events such as death, device exchanges, transplant, or recovery), and a high proportion of patient capture. These features strengthen the quality of the registry, but some limitations remain. Although the majority of patients are entered into the INTERMACS registry, patient inclusion requires informed consent, and some patients decline participation or are missed because of early postoperative death before obtaining informed consent (patients can be enrolled up to 2 weeks following device implant). The INTERMACS results could potentially be skewed if characteristics of patients not entered into the registry differ from those enrolled in the registry. It is also possible that some clinical outcomes may remain undetected, which may bias findings, although audits and data queries are part of the INTERMACS process. Such bias would have important ramifications if the data are used as a comparative control. Outcome data from INTERMACS are likely to be less robust than that generated from a clinical trial where formal clinical endpoint adjudication committees are often used. It may be highly desirable to have access to the details surrounding clinical and adverse events, because, as mentioned, future device advances will probably be realized in terms of lower adverse event rates rather than improvements in survival. In INTERMACS, it is impractical to review all adverse events, based on the sheer volume of events generated in these severely ill patients. Thus, use of INTERMACS as a control population may not be feasible for trials where event details in the control arm are critical. In addition, FDA access to the patient-level adverse event information is necessary for such trials, and accessibility to INTERMACS data need to be agreed upon by all parties. Finally, because INTERMACS is a real-world registry, standards of care are not controlled as they are in a clinical trial. Thus, different institutions may approach anticoagulation therapy or infection management differently, and these differences have the potential to confound data interpretation. Finally, patients receiving investigational devices are not enrolled in the INTERMACS registry, a point that raises issues regarding completeness of the population receiving these devices.

Registry data may be a reasonable control for trials of new devices in previously studied populations (eg, INTERMACS 1–3), provided risk and baseline characteristics are appropriately controlled with sound statistical methodology. However, comparison to registry data alone will be inadequate for the study of novel device designs or novel patient populations. Registry data are valuable for conducting hypothesis generating analyses to determine the threshold for which randomized analysis would be required (eg, at what INTERMACS patient profile is optimal medical therapy superior to VAD, or at what INTERMACS patient profile does the risk of adverse events outweigh the potential for clinical benefits).

Comparison with registry data may be accepted as a substitute for a randomized controlled trial, but a broad decision on the acceptability of this approach for all devices across all trials cannot be made by the FDA. Specific details must be known before a regulatory decision on the appropriateness of this approach can be reached, particularly with regard to the proposed population to be studied and proposed methods of matching population risk. Although the FDA acknowledges the promise of INTERMACS, they also point to the persistent challenges of selecting an accurately matched control population. Despite the position that registry data may serve as an acceptable comparator in appropriate situations, FDA and other key stakeholders must remain integrally involved in the study design process. Presubmission meetings are critically important to achieve consensus on the design and methodology of trials anticipated to result in approval of a device or expansion of an indication.

**Endpoint Considerations in Trial Design**

As noted, further advances in MCS therapy are likely to be realized in terms of device durability and lower adverse event rates, rather than in incremental improvements in survival. For this reason, survival alone will be an insufficient endpoint for future trials due to sample size requirements impacting cost and duration. Composite endpoints that integrate survival and functional assessments are likely to become more common in MCS trials. Clinicians and regulators continue to discuss the most relevant functional endpoints for VAD trials. Cardiopulmonary exercise testing with determination of maximal oxygen uptake (VO₂) and VE·VCO₂ slope has been demonstrated to be a powerful predictive tool in heart failure trials.²⁰ The value and prognostic importance of this test in the VAD population has not been validated. Six-minute walk is a standardized and validated measure of functional capacity that is more reflective of the activities of daily living. In an analysis of the HeartMate II BTT and DT pivotal trials, 6-minute walk distance improved significantly from baseline.²¹ Other, more subjective measures of functional status (New York Heart Association functional class, patient reported exercise ability) and quality of life (Minnesota Living With Heart Failure, Kansas City Cardiomyopathy Questionnaire) also improved in this analysis.²² However, important limitations exist to the use of these endpoints in the clinical evaluation of VAD therapy. Six-minute walk can be influenced by external factors and is a submaximal exercise test. Subjective measures of quality of life or functional status are inadequate primary endpoints in unblinded trials due to the potential for bias. Peak VO₂ is often preferred by the FDA, but it also has limitations related to data interpretation when patient effort and performance are inadequate. Historically, the pitfalls of cardiopulmonary exercise testing have been observed in device trials, with cardiac resynchronization therapy being the best example.²²⁻²⁴ Cardiac resynchronization therapy has unquestionably been shown to provide survival benefit, while the improvements in peak VO₂ have been variable and enrollment has been challenging.²²⁻²⁴ For these reasons, such measures may not be accepted as primary measures of efficacy by the FDA, but they may be informative as secondary measures of functional status or overall health status. Currently, there is lack of consensus regarding the most appropriate functional test to use in VAD trials. For INTERMACS to serve as a meaningful comparator in future VAD trials, functional assessments need to be collected and recorded at a level commiserate with a clinical trial. Efforts are under way to obtain robust benchmarks of functional capacity in INTERMACS.
Current and Future Role of INTERMACS in MCS Evaluation

Registries such as INTERMACS, Medical Arm of Mechanically Assisted Circulatory Support (MEDAMACS), and International Society for Heart and Lung Transplantation International Mechanical Assisted Circulatory Support Database (IMACS) have the potential to contribute clinically meaningful data in a more efficient manner than randomized trials in appropriate situations. In addition, INTERMACS is becoming integral to patient management by providing center-specific data and quality assurance reports to implanting centers and providing deidentified device-specific data to industry partners. Adequate and sustainable funding must be committed to support the infrastructure and resources required for data collection and analysis that is robust and of superior quality. The NIH, implanting centers, and industry have been instrumental in financially supporting INTERMACS. This collaborative effort is likely to sustain INTERMACS in the near future.

It is recognized that limitations in methodology exist for any study that is not prospectively designed as an adequately powered, controlled, randomized trial. However, alternative designs can be used that meet regulatory standards and produce clinically relevant data. Pre-planning, involvement, and cooperation of academic researchers, statisticians, regulators, payors, and industry are necessary to minimize these limitations associated with alternative designs to the extent possible.

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 DT and inadequate to study new device indications.

5. The INTERMACS registry 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 $V_o_{2\text{max}}$ 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 non-clinical 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

Is It Clinically Necessary to Distinguish Among DT, BTT, and Bridge to Decision/Candidacy?

The implant strategies and indications for the use of durable MCS devices for the treatment of advanced heart failure currently include BTT 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 BTT, bridge to decision or candidacy (BTC), 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. Patients classified as BTC do not differ greatly from those classified for BTT indication. Patients classified as BTC may have more intermediate risk factors (obesity, chronic obstructive pulmonary disease), but they tend to be of similar age as BTT patients. Thus, patients classified as BTT or BTC should not be viewed as two distinct populations, but rather as patients on a continuum of transplant eligibility. In contrast, patients designated for DT tend to be older and have more comorbidities than patients designated for BTT or BTC. These patients are more often hemodynamically stable and not in acute cardiogenic shock, generally reflecting an advanced, but chronic, heart failure population. These differences have the potential to influence therapeutic response or adverse events. These patients require long periods of support due to nonmodifiable comorbidities such as advanced age. This prolonged treatment places patients at greater risk of adverse outcomes.

Data from INTERMACS suggest that 20% of patients originally receiving MCS as a BTT still remain on device support 18 months after implant. Similarly, 20% of patients who were originally classified as DT subsequently underwent heart transplantation. In the recent INTERMACS analysis, the most commonly cited indication for VAD implantation was “BTT;” an indication that is not recognized from a regulatory (eg, FDA) or reimbursement (eg, CMS) perspective. Using transplant candidacy as a criterion for MCS therapy is challenging because a patient may be ineligible at the time of MCS implantation, but they may become eligible as a result of resolution or occurrence of comorbid conditions or patient choice. Mechanical circulatory support sustains life and, in many cases, allows patients to achieve physical and nutritional rehabilitation. Often, transplant eligibility can only be determined after a patient has undergone a period of VAD support. Alternatively, some patients initially implanted as BTT may subsequently experience either recovery of ventricular function and undergo device explantation or experience complications during VAD support (eg, disabling stroke) that may make them inappropriate or ineligible for heart transplantation. These examples underscore the fact that transplant eligibility is a dynamic rather than a static consideration and must be continually reevaluated with changes in the patient’s clinical condition.

A second inconsistency with the current indications of BTT and DT is the recognition that patients who meet criteria...
for heart transplantation and undergo VAD implant as BTT do not require a specific duration of symptoms before application of MCS therapy. The absence of duration of symptoms as a criteria for MCS therapy for BTT indication appropriately reflects the dynamic state of heart failure where patients can irreversibly decompensate from less severe states of heart failure in unpredictable or short time periods of time. However, for the indication of DT, requirements for duration of symptoms of heart failure or requirements on the duration of specific treatments inconsistently prevent appropriate candidates from receiving life-saving MCS therapy because of mandates on durations of symptoms or treatments (eg, inotropes or intra-aortic balloon pump therapy) that can adversely affect patient safety and outcome. Current CMS criteria for DT require demonstration of New York Heart Association class IV symptoms for 45 of 60 days or continuous inotrope therapy for 14 days or continuous treatment with an intra-aortic balloon pump for 7 days. If clinical deterioration where to continue despite these therapies, and a patient has not yet met the current duration of symptom or treatment guidelines, the patient would not be a candidate for VAD therapy.

The uncertainties of transplant candidacy frequently lead to challenges in determination of the precise indication for VAD placement. It is also important to recognize that these classifications are not mutually exclusive. Patient preferences may change over time. A durable device that improves functional capacity, quality of life, survival free of hospitalizations, and has an acceptable adverse event profile may be more attractive to a patient than heart transplantation, with the accompanying complex drug regimens and risk of rejection. Other nonclinical factors may also drive decisions to categorize patients as BTT, which further contributes to the creation of a nonhomogenous population. Advanced heart failure is a highly dynamic illness, and the management approach should be dictated by the patient’s clinical condition rather than arbitrary distinctions. An indication for MCS device implant that was broader, encompassing both currently approved indications and takes into account the dynamic process of patient evaluation would provide more consistent application of VAD therapy to patients with advanced heart failure.

It has been proposed that MCS devices should be evaluated, approved, and reimbursed according to “short-term” (eg, devices not permitting patient discharge with untethered mobility) 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. The challenges of this approach are that there are important differences in baseline risk among BTT, BTC, and DT patients that translate into differences in outcome post-VAD implantation. The endpoints of interest for these populations differ and designing such a trial would be methodologically challenging but feasible.

A basic tenet of clinical research is to obtain a relatively uniform population so that the effects of an investigational device can be quantified with minimal confounders. The use of a single pivotal trial intended for regulatory approval as a long-term MCS device would enroll a broader patient population with varied baseline risk comprised of both BTT and DT patients. Recruitment to the investigational arm of the study would be relatively simple, as these patients are currently receiving VADs. Inclusion criteria could establish a minimum level of risk by using objective measures such as combinations of biomarkers, functional limitations, hemodynamic parameters, or multivariable risk models. A major trial design challenge is defining an appropriate control group. Novel strategies defining success of such a trial might include the achievement of predetermined objective performance criteria based upon prior BTT and DT trials.

The clinical endpoints and outcomes of interest are somewhat different among BTT and DT indications, and this may challenge the appropriateness of eliminating these distinctions. For BTT, short-term (eg, months) outcomes such as survival to transplant are very meaningful and important to quantify, as well as long-term post-transplant survival outcomes. Quality of life is also very important, but quality of life assessments can be confounded by the focus on the final endpoint of transplantation. For DT (eg, support for more than 2 years), survival is important, but quality of life and functional status measures are of equal importance, as patients will be living with the devices for extended periods. Future trials will need to be designed with adequate power to assess clinical outcomes and health status measures. Transplant rates and competing outcome events must also be dealt with in any endpoint analysis.

As MCS devices are investigated in less sick populations, conducting a single trial will become increasingly difficult. Operational and data quality issues pertaining to patient crossover rates or changes in treatment strategies will arise, and it will be difficult to design a trial to account for these issues because these event rates are not well characterized. Just as separate clinical trials have been conducted according to heart failure severity for drugs and non-MCS devices, it may be that separate clinical trials will continue to be needed for MCS to address these challenges.

Although clinically challenging, the distinction between BTT and DT developed out of the clinical concern of permanently implanting a new technology into patients who were without other options should the device fail. The BTT indication also provides an opportunity for industry to gain short-term market experience with the device before expanding to longer term use. The BTT indication is attractive for new device development for that reason. To move toward a single indication, appropriate consideration needs to be given to early phase development and the requirements that are needed to ensure reasonable confidence in the safety of new technology. A trial design allowing early (eg, 6 months) and late (eg, 2 years) assessment of outcomes may be a feasible approach to achieving these goals. The complexity of the field does not support a “one size fits all” approach to clinical trial design. However, it may be useful to propose standard clinical trial design template approaches that could be applied consistently in specific situations. To promote advancements in this area of MCS device development, ideas and discussion among FDA, sponsors, investigators, and payors is necessary. In some circumstances, it may be feasible to
combine indications in a single clinical trial, but the specific details must be determined and agreed upon by key stakeholders. Pre-submission meetings are one forum where such discussions could take place. A broader strategy may involve submission of potential study designs or templates to FDA that could be posted for stakeholder comment, with meetings to further discussions and develop common strategies.

How Do Stakeholders Achieve Consistency Across Regulatory and Reimbursement Decisions?
Before BTT and DT indications can be eliminated in favor of a unified long-term MCS indication, common ground between approved indications and reimbursement indications must be established. Nationally covered indications include BTT or DT. For new devices seeking a single indication, involving CMS early in the clinical trial development process, along with FDA is key to achieving consensus among regulatory and payor stakeholders.

Summary Opinion
1. The current indications of BTT 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, clinicians, and CMS) 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 (PMAs) 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
Can International Experience Be Leveraged to Foster VAD Innovation and Development in the United States?
Exporting operational components of clinical research is not unique to VAD clinical trials. A systematic review of 123 studies that supported 78 PMAs for a variety of cardiovascular devices from 2000 to 2007 revealed that 27% of the studies were conducted entirely outside of the United States. Several practical reasons for this trend exist. 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 Européenne (CE mark) that is required for marketing in the European Union can be obtained more quickly, with lower costs and less complexity compared with the United States. Importantly, the CE mark is accepted in other countries within the European Union, whereas the PMA used by the FDA is only applicable to the United States. From an industry perspective, time to commercialization is an important consideration that influences study conduct.

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.

United States Standards
In the United States, valid scientific evidence that provides reasonable assurance of safety and efficacy of a device is required to obtain PMA for high-risk medical devices. Assurance of safety and efficacy involves preclinical data to establish component durability, electrical safety, electromagnetic compatibility, software functionality, and biocompatibility among other issues, followed by a clinical trial conducted under an investigational device exemption. A clinical trial must be designed to demonstrate safety and effectiveness of clinical outcomes or of quality of life. The PMA process is currently the most rigorous, and therefore the most burdensome, among countries where MCS is being tested and implemented. The regulatory approval cycle is currently longer than device development time, and this substantially limits the ability to move the field and technology forward. In the United States, approval of one device is often pending, while trials of the next device iteration (with improvements) are already beginning in the European Union. The preclinical and pilot studies require substantial time to conduct, and result in significant delays in time to market. These studies are critical to demonstrate safety for innovative or unproven first-in-human devices. To circumnavigate this challenge, many companies will seek approval in the European Union first and use some or all of the EU data to meet the feasibility requirements of the FDA where allowable. The FDA has recently issued guidance on first-in-human initiatives for device evaluation. However, from the FDA perspective, if data quality are lacking, then new preinvestigational device exemption studies will still be required. Further, for EU or Japanese data to be extrapolated to the United States, it must be determined that the populations are similar and would be expected to respond similarly to the device. Establishing the definition of “similarity” with confidence may be challenging. Environmental, socioeconomic, practice patterns, standards of care, and penetration of guideline adherence are important determinants of MCS outcomes.

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.

The FDA recently released their 2012 strategic plan, and by the end of the year, the FDA plans to publish a proposed rule that clarifies when the Center for Devices and Radiological
Health will accept data from clinical studies conducted in and for other countries, as well as have mechanisms for exchange of medical device information with foreign regulatory authorities. Harmonization of standards across countries is an important issue that is currently lacking, but needs to be addressed in order for data exchange to be meaningful. The FDA has piloted a “Harmonization By Doing” Program and has worked with regulatory agencies in Japan to collaborate on the review of VADs.\(^3\)

Postmarketing surveillance of medical devices has also come under scrutiny.\(^3\) The field of MCS has been successful in establishing a robust infrastructure to support postmarketing analysis through the INTERMACS registry. Changes in the FDA’s approach to postmarketing surveillance are under development in an effort to address limitations in postmarketing surveillance and improve the ability to ensure postmarketing safety of medical devices.\(^2\)

**European Standards**

In the European Union, the medical device approval process is driven by directives rather than by an overall authority. The process requires data to demonstrate that a device meets specified standards, and these data are reviewed by an independent notifying body. These bodies are independent, and although they are monitored by their member country, variation exists across these organizations. Some limitations to the notified body system exist, including the fact that a portion of their support is generated from fees paid by device manufacturers. In some situations, sponsors can also pay a higher fee for accelerated review. Whether these factors bias the review process has not been well explored. Human clinical investigations are required, but there is no mandate to conduct randomized trials that assess clinical outcomes. Data must show that the device performs as intended, but “as intended” could be measured by improving hemodynamics, cardiac output, or some other mechanic measure.\(^5\) This bar is much more achievable with fewer patients and a shorter time frame than that required for FDA PMA. Comparison to an existing control is not required. The notifying body then grants approval for labeling with the CE mark. This mark allows the device to be distributed throughout the European Union. Because approval in the European Union is based on performance and safety, the studies can generally be shorter and involve fewer patients, leading to faster approval times. It should be noted that no MCS device has been withdrawn from the EU market because of safety concerns. The European Society of Cardiology held a policy conference that developed several recommendations for reform of the European medical device approval process.\(^2\)

**Japanese Standards**

In Japan, the regulatory process is young and evolving. The initial application process is often very lengthy, requiring 12 to 18 months for approval. Similar to the United States, approval requires demonstration of both safety and efficacy, but the required sample sizes are much smaller (15 cases for a pivotal study and 5 cases for a feasibility study).\(^3\) These sample sizes are not hypothesis driven sample sizes, but are generally used to evaluate safety and ensure instructions for use have been appropriately translated. The process for approval of device modifications in Japan is more complex than in other parts of the world and can also be a lengthy process.

**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 outside the US patient data are warranted.

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

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**

**Can a Standard of Preclinical Testing Be Established to Identify Failure Modes and Device Longevity?**

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.\(^3\) These standards direct developers to focus on a system’s most critical potential faults (eg, external power cables, percutaneous leads, or other peripheral component failures), and to plan for appropriate mitigations should such failures be detected (eg, design changes, production test coverage, training). The development of robust preclinical testing 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.

Accelerated component reliability testing should demonstrate long-term durability before regulatory submission with the expectation that device longevity should exceed expected use in clinical trials and clinical use. The potential long-term use of MCS devices requires test durations that exceed the length of clinical trial follow-up. Thus, reliability testing may begin in the preclinical arena and continue for the duration of clinical trials and into the initial marketing experience. Owing to the anticipated duration of clinical use of MCS devices, demonstration of durability for 5 years or more is reasonable for extended run time tests. This expected level of performance is longer than the FDA’s current 2-year requirement for destination therapy.

The advent of novel devices introduces new reliability issues. Patient mobility is enhanced with the newer, smaller devices, but this may lead to reliability problems that were not
Biological Reliability and Human Factor Concerns
An ongoing and major challenge facing preclinical testing is the assessment of MCS device biological reliability and pertains to the device–patient interface. Findings from preclinical testing in animal models or mock loops may not be clinically relevant to the experience in humans and clinical problems may arise after device implantation that were not anticipated or signaled by preclinical testing. A highly pertinent question is what occurs at the device–patient interface? What types of use and daily activities may promote device failure? Biological reliability includes uncontrollable forces due to patient comprehension of use and maintenance, unpredictable trauma from environmental factors, as well as patient activity for which preclinical testing models may have been insufficient. 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. Devices are generally tested according to their expected conditions of use. Attempts are made to identify failure modes using excessive loading conditions or accelerated testing. However, identifying clinical conditions or patient activities that would result in these extreme failure conditions are difficult to identify or anticipate. Thus, being able to generate data describing clinically relevant failure modes of MCS devices could help anticipate when components may need to be replaced or repaired, and increase the margin of safety associated with real-life device use. This process of evaluation could be used to improve education of physicians and patients on proper use to mitigate risk.

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 (HDE) program. The HDE program facilitates development of devices when the intended population to treat is fewer than 4000 patients annually. The HDE has a lower standard than does the PMA process and does not require demonstration of effectiveness, but sufficient data must be included to allow the FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury from its use. Fostering device development for the pediatric population has been an important initiative by the NHLBI and 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-corpooreal membrane oxygenation systems and two VAD systems for pediatric patients with advanced heart failure.

Challenges Facing Pediatric MCS Device Development
Pediatric MCS device development faces unique challenges, as well as challenges common to adult MCS. Mechanical circulatory 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 HDE 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. The level of probable benefit required of a new device will be dependent on the patient population under study and alternative treatment options. 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 (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 where neurologic assessment of 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.

**Fostering Device Development in the Pediatric Population**
The size of the intended population to treat with pediatric MCS devices is small, providing little incentive for the medical device industry to invest in significant research and development of innovative products for this population. An attractive strategy to foster device development for pediatric applications would be to encourage the application of pediatric findings to applications in the adult population in the form of miniature partial support devices or small pumps for right-side heart support applications. The larger intended population to treat would provide sufficient return of industry investment in the development of MCS devices for pediatric applications.

**Unmet Needs in Pediatric MCS**
The FDA-approved devices for pediatric MCS, the MicroMed DeBakey Child and the Berlin Heart EXCOR, are used primarily for patients with cardiomyopathy awaiting cardiac transplantation. A continuing unmet need for pediatric devices is in the population with complex congenital heart disease, including those with a single ventricle physiology. Postcardiotomy patients needing short-term support for recovery after open-heart surgery are also a potential population, but MCS options do not currently exist for these patients. The congenital population is another under recognized group for which support options will be needed as the patients reach adulthood. The population of pediatric patients in need of MCS has not been well characterized. The proportion of patients who need left ventricular assist device versus biventricular assist device support is not known. Further, it is likely that some patients could benefit from right ventricular assist device only support, but this approach has not been explored.

The ability to promote patient recovery without the need for heart transplantation may represent a major advance for pediatric patients. Additionally, DT that could replace the multiple transplants faced by the patients over the course of their lifetimes could have several potential advantages, ranging from reductions in morbidity to reductions in cost related to avoidance of multiple transplants. These areas should be the focus of future research.

The pediatric experience to date has shown that these patients can be successfully bridged to transplant with MCS. Since this has been established, other outcomes need to be evaluated in future trials (ie, neurodevelopment outcomes, quality of life). Similar to the challenges in the adult population, there are limitations to the comparator groups used in pediatric MCS trials. In the Berlin Heart Trial, historical controls receiving extracorporeal membrane oxygenation were used from the Extracorporeal Life Support Organization registry, since extracorporeal membrane oxygenation has been the standard of care for MCS for patients failing medical therapy for more than 20 years. However, as with the adult population, historical controls are limited because they do not reflect changes in patient selection over time.

More work is needed to obtain registry data on the pediatric population, so that current demographics, clinical characteristics, and outcomes of the population can be described. Data from compassionate use of the EXCOR VAD are one source, but enrolling pediatric patients into INTERMACS/PEDIMACS represents another option. Currently, there is limited pediatric participation in INTERMACS. As the field advances, more attention to clinical adjudication in INTERMACS would be important.

**Summary Opinion**
1. Expected “probable benefit” for device therapy in the pediatric population needs to be defined.
2. Focus should be placed on areas where 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 to describe the clinical characteristics and outcomes of pediatric patients is needed.
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 in this country. 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

The authors report the following disclosures: Keith D. Aaronson, MD, research support and speaker fees from HeartWare International, Inc; Michael A. Acker, MD, consultant for Thoratec Corporation; Timothy Baldwin, PhD, no disclosures; Steven Boyce, MD, educational grants from and stock ownership in Thoratec Corporation and Heart-Ware International, Inc; Elizabeth Blume, MD, no disclosures; Mariell Jessup, MD, research on investigational mechanical support from Thoratec Corporation and Heart-Ware International, Inc; Timothy Baldwin, PhD, no disclosures; Steven Boyce, MD, educational grants from and stock ownership in Thoratec Corporation and Heart-Ware International, Inc; Elizabeth Blume, MD, no disclosures; Mariell Jessup, MD, research support from Thoratec Corporation and Heart-Ware International, Inc; Michael A. Acker, MD, consultant for Thoratec Corporation; Randall C. Starling, MD, MPH, member ROADMAP Steering Committee; Douglas L. Mann, MD, no disclosures; Leslie Miller, MD, no disclosures; David Nafteil, PhD, Berlin Heart, Inc and HeartWare International, Inc; Francis D. Pagani, MD, PhD, national principal investigator, Heart-Ware Endurance trial; Mark S. Slaughter, MD, training and educational grant support from Thoratec Corporation and Heart-Ware International, Inc; Randall C. Starling, MD, MPH, member ROADMAP Steering Committee, and travel reimbursement (≤$5000 per annum) from Thoratec Corporation; Lynne Stevenson, MD, no disclosures; Wendy Gattis Brugh, PharmD, no disclosures; Jeffrey Teutcher, MD, no disclosures; Peter Wearden, MD, PhD, no disclosures; Stephen Westaby, MD, PhD, Medical Director, Calon Cardiotechnology Corporation (uncompensated); and Clyde Yancy, MD, no disclosures.
Statement Regarding the Pre and Post Market Assessment of Durable, Implantable Ventricular Assist Devices in the United States

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Circ Heart Fail. 2013;6:e1-e11; originally published online November 12, 2012; doi: 10.1161/HHF.0b013e318279f6b5

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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