

## HFSA Position Statement

# Key Issues in Trial Design for Ventricular Assist Devices: A Position Statement of the Heart Failure Society of America

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Heart failure represents the one major form of heart disease that continues to increase in prevalence, both in the United States and worldwide. There are presently estimated to be 4.9 million patients in the United States with heart failure, with 550,000 new cases per year, representing the primary diagnosis for approximately 999,000 hospital discharges in year 2000.<sup>1</sup> Over the past decade, significant gains have been made in drug therapy for heart failure, with angiotensin converting enzyme (ACE) inhibitors and beta-blockers providing significant reduction in morbidity and mortality. Nevertheless, over 250,000 annual deaths are at least partly attributable to heart failure.<sup>1</sup>

For patients with advanced heart failure, life expectancy and health-related quality of life (H-QOL) may be identifiably limited, despite optimal medical therapy. Until recently, the only additional available treatment for these patients was cardiac transplantation, a procedure performed approximately 2,155 times in the United States in 2002, with donor availability being the limiting factor.<sup>2-7</sup>

In recent years, there have been major advances in device technology and its clinical impact in patients with advanced heart failure.<sup>8,9</sup> Major categories of devices that are either available or are under development include 1) devices that assume some or all of the work of the heart (ventricular assist device—VAD); 2) devices that electrically resynchronize ventricular contraction (biventricular pacing); 3) devices that reverse life-threatening ventricular arrhythmias (implantable cardiac defibrillator—ICD);<sup>10</sup> 4) devices that unload the heart; 5) devices that impede adverse cardiac remodeling;<sup>11</sup> and 6) devices that monitor cardiac function

and/or hemodynamics. These devices have posed major challenges in the design of clinical trials for demonstration of clinical efficacy.

On February 26 and 27, 2003, the Heart Failure Society of America held a workshop entitled “Key Issues in Trial Design for Devices in Heart Failure.” The workshop included participation by representatives of the American Society for Artificial Implantable Organs, the International Society for Heart and Lung Transplantation (ISHLT), the North American Society for Pacing and Electrophysiology, and the Society for Thoracic Surgery. Also in attendance were individuals from the US Food and Drug Administration’s (FDA) Division of Cardiovascular Devices, the Centers for Medicare and Medicaid Services (CMS), the National Heart, Lung, and Blood Institute, and the medical device industry. The first day focused on VADs, and the second day focused on cardiac resynchronization devices.

It was not intended that the conference would generate comprehensive recommendations regarding trial design. Rather, the focus was to initiate dialogue among interested and knowledgeable parties from the arenas of clinical science, public health, government regulation, and industry; identify areas of consensus; and move the field forward. Specific goals were:

1. to establish dialogue among the various constituencies;
2. to identify points of consensus;
3. to identify areas requiring additional analysis and dialogue;
4. to encourage device development, while establishing a rational basis for approval and coverage;
5. to establish a forum for ongoing progress;
6. to identify areas where further research is needed.

This report represents a position statement of the Heart Failure Society of America, based on the proceedings of one aspect of the workshop: ventricular assist devices (VADs). The opinions are those of Heart Failure Society of America.

The discussion was divided into the 2 principal indications for VADs at the present time: 1) as a means of supporting life while the patient who is poorly responsive to medical treatment awaits cardiac transplant (bridge-to-transplant),

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<sup>1</sup>This statement was reviewed and approved by the HFSA Executive Council (Appendix 1).

Based on Proceedings of a Joint Workshop, February 26, 2003. The opinions expressed are those of the Heart Failure Society of America.

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and 2) as definitive treatment for patients with severe heart failure, who are poorly responsive to medical treatment (destination treatment). (Currently, destination therapy is considered appropriate only for patients who are not candidates for transplantation.)

A number of specific issues were identified that present challenges to the design of trials to evaluate efficacy and safety of VADs.

- First, advances in the design of these devices are likely to come incrementally, and it is challenging to determine which changes necessitate a clinical trial to establish safety and efficacy.
- Second, the inability to blind trials and the potential for randomization to no device present an emotional burden to the patient, impedes enrollment, and provokes high potential for drop-outs and cross-overs, hampering endpoint analysis.
- Third, limited availability of subjects and experienced centers restricts the size of trials that can realistically be performed for either “bridge-to-transplant” or “destination” therapies.

### Ventricular Assist Devices as Bridges to Cardiac Transplant

#### Population

It is important to define the target population for VADs as bridges to cardiac transplant, particularly in considering the design of trials in which objective performance criteria are used instead of comparing outcome endpoints between populations receiving active treatment and concurrent controls.

The target population for a prospective trial of a VAD as a bridge to transplant is composed of patients with a high likelihood of mortality prior to availability of a donor heart.<sup>12</sup> The benefit of VAD for bridging the sickest patients has never been tested but is assumed for some patients, in whom randomization probably can never be performed. Therefore current delineation of a target population of potential transplant recipients with improved survival following VAD implant, compared with medical therapy alone, is based on expert opinion, rather than prospective, randomized-controlled data. Furthermore, each of the elements that impact on the nature of the appropriate target population—characteristics of the recipient population, the nature of medical therapy, physical characteristics of VADs—is undergoing continuous change.

**Population Shifts.** Over the past two decades there has been a progressive shift in the population undergoing cardiac transplant. Patients undergoing transplant are now older and sicker, have more comorbidities (including diabetes, renal dysfunction, advanced atherosclerosis, cachexia, and secondary pulmonary hypertension),<sup>13,14</sup> and are more likely to be receiving intravenous inotropic or vasoactive drugs.<sup>15-7</sup> Reasons for this shift include: 1) improved medical therapy,

obviating consideration of transplant for any but the sickest patients; 2) increased surgical and medical transplant proficiency, resulting in acceptable transplant outcomes in higher-risk patients; 3) decreased donor availability,<sup>18</sup> resulting in reduced likelihood for transplant in the absence of intravenous infusion therapy and/or mechanical assist (conferring higher recipient priority status); and 4) broader candidacy for third party reimbursement for transplantation. Such population shifts make it particularly problematic to identify performance targets within prospective clinical trials.

**Shifts in Concomitant Treatments.** Medical and device therapy for severe heart failure is evolving. Significant impairment of renal function—a prominent characteristic of the population of patients with advanced heart failure—has diminished in importance as an absolute contraindication for ACE inhibition.<sup>19-21</sup> Patients intolerant to ACE inhibitors are now routinely treated with angiotensin receptor blockers (ARBs).<sup>22</sup> As a result of recent clinical trials<sup>23</sup> and clinician experience, beta-blockers are increasingly used among patients with severe heart failure.<sup>24</sup> Aldosterone antagonists, when tolerated, are routinely used in patients with severe heart failure.<sup>25</sup> The vasoactive agent, nesiritide, is increasingly being used in addition to, or in place of, inotropic agents (although the impact that this shift has on survival is unknown).<sup>26,27</sup> Implantable cardioverter-defibrillators (ICDs) and resynchronization devices are being increasingly implanted in this population.<sup>28</sup> Although it is difficult to know the precise impact that these treatment shifts are having on clinical outcomes, there is evidence both from results of sequential heart failure clinical trials and from epidemiologic surveys that survival in patients with heart failure is improving.<sup>29-32</sup> These shifting population characteristics, in terms of disease severity, comorbidities, and antecedent or concomitant medical treatment have unknown impact on outcomes following VAD implant. Actual and perceived effects of medical therapy may shift the VAD population to one of increasing morbidity and worse outcome, an effect that may be countered by a perception of improved VAD performance and increased clinician experience.

**Evolution of Devices.** As devices evolve, with improved reliability, improved ease of implant, increased patient acceptability, and providing the potential for reduced morbidity and mortality during and following implant, the likelihood exists for increasing the difference in outcomes with and without VAD implant. Under such circumstances, it may be reasonable to consider expanding the target population to patients who are less critically ill. Such improvements also imply that VADs will begin to compete with cardiac transplantation with regard to anticipated survival, and the distinction between the “bridge-to-transplantation” and “destination” indications will blur. Under these circumstances of an expanded target population, objective performance measures become less informative as indices of efficacy, and prospective, randomized, controlled trials become increasingly necessary in judging the clinical impact of a particular VAD.

**Inclusion Criteria for Clinical Trials.** Clinical objective performance criteria for evaluating the safety and efficacy of VADs implanted as bridges to transplant will be drawn from existing published series of patients in whom these devices were implanted. For this reason, at the present time, attempts should be made to match those characteristics known to impact outcome of populations targeted for trials of newer devices for this indication with those of patients within those series. Substantial challenges exist in identifying appropriate comparative populations to yield performance targets against which to match results of prospective investigations. In general, assumptions regarding the predictability of event rates for prospective populations, compared with historical controls, are fraught with error. A number of examples may be cited in which populations with characteristics carefully chosen to match those of a historical study group yielded substantially different cardiovascular event rates.<sup>33</sup>

**Table 1** lists characteristics for consideration in attempting to construct entry criteria and to match populations targeted for prospective clinical investigation with ones from which objective performance criteria may be derived. Each of these items has been identified within one or more multivariate analyses as predictive of mortality risk.<sup>34,35</sup> Higher risk is conferred, for example, by 1) advanced age,<sup>36</sup> 2) ischemic etiology,<sup>37</sup> 3) NYHA class IV,<sup>37</sup> 4) diabetes,<sup>38,39</sup> 5) creatinine > 2 mg/dL (or estimated creatinine clearance < 60 mL/min),<sup>40–2</sup> 6) history of sustained ventricular tachycardia or ventricular fibrillation,<sup>43,44</sup> and 7) use of continuous or intermittent intravenous vasoactive agents as an outpatient.<sup>45</sup>

In considering patients for enrollment in clinical trials investigating VADs as bridges to heart transplant, it is appropriate to require that patients continue to be symptomatic at rest or with minimal exertion and/or clinically unstable (eg, respiratory distress and/or reduced tissue perfusion) despite maximal tolerated medical treatment, including intravenous inotropic and/or vasodilator treatment. Maximal oxygen consumption during treadmill exercise is frequently used as a means for estimating disease severity and risk. However, most patients under consideration for VAD as a

bridge to transplant will be unable to undergo exercise testing.<sup>46,47</sup> Questionnaires that assess clinical status or H-QOL may prove useful for further stratifying risk across a population of interest.<sup>48</sup> To date, most data from such questionnaires are derived from ambulatory populations, although some information exists within hospitalized populations.<sup>48–53</sup> Future analysis of H-QOL data from such populations may improve our ability to match historical and target heart failure populations.

Strong consideration should be given to using the severity and directional change over time of renal functional impairment, despite maximal medical treatment, as a means for estimating the risk in a target population and for matching that risk to a historical group. Altered renal function is increasingly recognized as a marker of both diuretic resistance and adverse clinical outcome (persistent and/or recurrent need for hospitalization; mortality).<sup>36,40–2, 54–7</sup> Estimates of creatinine clearance, incorporating serum creatinine, age, gender, and body weight (Cockcroft-Gault equation<sup>58</sup>), may be superior to serum creatinine alone as a marker of reduced renal function and of adverse clinical outcomes.<sup>41,59–61</sup> A caveat to these calculations is that excess total-body fluid can yield spuriously high estimates of creatinine clearance; incorporating an estimate of dry weight, where possible, is likely to provide more accurate assessment of creatinine clearance. There is no universally accepted definition of “worsening renal function” which could be used to better define a population whose renal function is deteriorating and could benefit from a VAD. Inability to tolerate ACE inhibitors and/or beta-blockers represents an additional characteristic of patients with hemodynamic instability and is likely to denote worse prognosis.<sup>62</sup>

## Trial Design

Patients who manifest symptomatic hypotension and/or diminished end-organ perfusion despite optimization of filling pressures and treatment with intravenous inotropic and/or vasoactive agents have a high short-term risk for mortality. There is widespread acceptance that the current generation of VADs improves the likelihood of survival to transplant in this population.<sup>63</sup> For this reason, it is appropriate to encourage application of objective performance measures within uncontrolled trials of newer VADs, as an alternative to trials in which VAD and medical therapy are prospectively compared,<sup>64</sup> as long as the target population remains similar to that for which the current generation of VADs is indicated as bridging devices.

Objective performance measures are pre-established criteria identified as sufficient to infer clinical safety and efficacy, based on information from previously investigated populations. These criteria represent presumed characteristics of an inferred active-control population. Under select circumstances, their use within an uncontrolled trial may be considered in place of a concurrent, randomly assigned control population. Performance measures based on existing historical data should be applied only to the sickest populations

**Table 1.** Distributional characteristics to be approximated in comparing prospective and historical populations for generating objective performance measures

1. Age<sup>36</sup>
2. Gender<sup>37</sup>
3. Etiology<sup>37</sup>
4. Left ventricular ejection fraction (or degree of ventricular dilatation)<sup>43,77,78</sup>
5. Functional status, as defined by NYHA Class; H-QOL assessment; or exercise testing<sup>43,46,47,48,79</sup>
6. Diabetes<sup>38,39</sup>
7. Severity of renal insufficiency<sup>40,41</sup>
8. Serum sodium<sup>80</sup>
9. History of sustained ventricular tachycardia or ventricular fibrillation<sup>43</sup>
10. Use of ACE inhibitors for ARBs<sup>22,81</sup>
11. Use of aldosterone antagonists<sup>25</sup>
12. Use of beta-blockers<sup>82–4</sup>
13. Prior surgical history
14. Intravenous inotropic or vasoactive agents used<sup>45,85</sup>
15. Mechanical support devices used

that have traditionally been a target for bridge-to-transplant. Work is still needed in standardizing inclusion criteria, safety measures, definitions, and endpoint criteria for existing datasets and in developing prospective databases.

**Sources of Data for Generating Performance Targets.** A number of types of datasets represent potential sources for generating objective performance measures. The first is the published literature, a useful but limited source of information. Published literature is limited by a) potential publication bias, b) lack of standardization in definitions, endpoints, and reporting, and c) frequent absence of patient-specific data. Nevertheless, the published literature may presently represent the principal source from which comparative outcome results may be derived. Datasets used to support previous Pre-Market Applications represent a second potential source for generating objective performance measures. However, these data are proprietary and are not generally made available to support applications from competing device companies. Although highly challenging, it is worth pursuing achievement of an industry-wide agreement for limited use of these datasets and collation into definable performance targets. Prospectively collected clinical databases represent a third potential source of outcome data. Such databases could offer substantial advantage by pre-defining data to be collected regarding population characteristics and clinical outcomes; by broad inclusion of practicing sites; and by offering complete, primary data for analysis. The database of VAD recipients being developed by the ISHLT has substantial potential value as a source of outcome information for incorporation into objective performance criteria for future VAD trials. CMS has required database participation as a criterion for reimbursement for implant of VADs as destination therapy.

In designing trials of VADs as bridges to heart transplant, consideration may continue to be given to comparison with a prospectively randomized control population. Such consideration is particularly germane where less-sick populations are targeted by newer devices, with improved reliability, increased ease of insertion, and/or reduced anticipated morbidity. In investigating populations presently receiving medical treatment, randomization to a medical control group should be feasible. Alternatively, in sicker populations in which continuation of medical therapy alone is not a realistic option, consideration may be given to comparison with a group randomized to an approved VAD. Such a design poses a substantial challenge in selecting an endpoint, or combination of endpoints, for which non-inferiority may be achieved with a reasonable sample size. However, successful comparison with an approved device may yield a more convincing argument for approval than achievement of objective performance targets, where equivalence of the study population and the historical population (from which the performance targets were derived) may be challenged.

#### **Endpoints: Efficacy**

In investigating VADs as bridges to heart transplantation, the most commonly employed efficacy endpoint has

appropriately been survival to transplantation. Acceptable alternative endpoints are survival through and beyond transplantation (eg, over a period extending to six months post-transplantation) and survival of the patient with "neurologically acceptable" function. Endpoints appropriate for exploring efficacy of devices used as destination therapy may be less appropriate as primary endpoints where the principal purpose of implant is to improve the likelihood of the patient surviving long enough to undergo transplantation. For example, improvement in H-QOL or in exercise capacity is frequently employed to assess drug or device efficacy in heart failure clinical trials. If the efficacy of a VAD is specifically being explored as a device to improve the patient's chance of reaching cardiac transplant, then improvement in H-QOL or in exercise capacity are neither necessary nor sufficient to assert device efficacy. Measures such as H-QOL or exercise capacity are, however, reasonable as secondary endpoints. Furthermore, it is possible that developers of future VADs may seek claims of improved H-QOL, relative to previously approved devices, while simultaneously achieving pre-established requirements for performance, in terms of survival to transplant. It is also reasonable to consider minimal acceptable standards for H-QOL results or specific measures of physical function across a population receiving a VAD. Several H-QOL instruments have been well-validated in patients with heart failure, although additional work may be needed to validate existing instruments, or develop new ones, to both optimally apply to the sickest patients undergoing VAD placement and to consider H-QOL issues that may arise specifically from the presence of the VAD itself.

#### **Endpoints: Safety**

Major safety considerations for VADs include infection, bleeding, systemic thrombotic events, and neurologic deficits. It is appropriate to establish standards for the maximal acceptable frequency of these safety endpoints, based on findings from series of VAD recipients. There is a multifactorial potential for VADs to impact on neurologic function: 1) as a consequence of the implantation procedure, 2) through the direct impact of the device on cerebral blood flow, and 3) through discrete thrombo-embolic or hemorrhagic events. It is therefore important to establish standard definitions and objective diagnostic criteria for both the occurrence of discrete neurologic events and changes in neurocognitive function. The National Institutes of Health Stroke Scale is a widely accepted instrument for diagnosing and establishing the severity of vascular-based neurologic impairment.<sup>65,66</sup> At the present time, more data are needed before an acceptable standard for neuro-cognitive impairment can be established and incorporated as a primary safety endpoint within a prospective trial. As more data are accumulated, taking into consideration both the baseline brain state of these patients as well as the magnitude of post-VAD changes, such standards can be established.

## Ventricular Assist Devices as Definitive (“Destination”) Therapy

The distinction between development of VADs as bridge-to-transplant and destination therapy is rapidly blurring. Factors contributing to this loss of distinction include: 1) a decrease in donor availability, coupled with a growing prevalence of heart failure, resulting in increasing waiting times for transplant;<sup>67</sup> 2) the potential for a VAD to reverse a contraindication to transplant (including “irreversible” pulmonary hypertension and secondary organ system dysfunction); and 3) the prospect of development of VADs with greater reliability, diminished morbidity, and greater patient satisfaction, raising the possibility of a shift in goal from bridge to destination following implant, or implant with a later option for transplant. For these reasons, although the discussion group stressed issues and solutions specific to either the bridge or destination indication, in fact, many of these issues are becoming more and more generic to VADs, regardless of the stated indication.

### Population

The REMATCH study provides the first solid information toward defining a population that stands to benefit from the current generation of VADs applied as destination therapy.<sup>68</sup> The initial entry criteria for this study included: 1) NYHA class IV symptoms for  $\geq 90$  days despite maximal medical treatment, including ACE inhibitor, diuretic, and digoxin, and 2) maximal oxygen consumption of  $\leq 12$  ml/kg/min or “continued need for” intravenous inotropic therapy. Entry criteria were broadened late in the trial. However, the vast majority of patients enrolled met the original entry criteria.

To date, there has not been uniform agreement on the definition of the term “inotrope dependence.” Within the REMATCH trial, this term was initially defined as symptomatic hypotension, reduction in renal function, or worsening heart failure symptoms upon attempt at weaning.<sup>68,69</sup> It was later further defined as requiring evidence of two failed weaning attempts. (It should be noted that there is no one accepted process for weaning a patient from an inotrope.)

The recruitment experience in REMATCH provided direct evidence for the marked variability in treatment practice and in categorizing disease severity (as in application of the definition of inotrope dependency) across individual practitioners. The study employed a central medical “gatekeeper” in an attempt to maintain consistency of entry criteria and to assure that only patients who stood to benefit most from VAD implant were enrolled. Further perfection of this approach and its continued application appears indicated within future VAD trials.

Further work is needed to define criteria (beyond “inotrope dependency”) in stratifying survival likelihood as a means for identifying indications for VADs.<sup>12,64</sup> Various analyses have identified numerous factors linked to mortality risk. The principal ones are identified in Table 1, above. The severity of renal insufficiency and intolerance to treatments

such as ACE inhibition and beta-blockade may be helpful. However, shifts in the demographics of the heart failure population and changes in medical therapy advances—including drugs, devices, and system approaches to medical management—are likely to reduce mortality and/or alter the relation between previously identified risk factors and the likelihood of survival. For these reasons, it is imperative to continuously update the validity of predictive models. Furthermore, databases specifically directed toward patients who are potential candidates for VADs would provide invaluable insight into factors linked to adverse outcomes, while providing real-time insights into the impact of shifts in patient demographics and in treatment.

The severity of illness of patients enrolled into REMATCH was confirmed by the high mortality rate observed in the medical treatment arm: approximately 50% at six months and 75% at one year. These rates are considerably higher than in any previously performed prospectively controlled study in heart failure or in community-based surveys of patients hospitalized with heart failure.

A separate issue related to inclusion and exclusion criteria for trials of VADs as destination devices relates to defining contraindications for heart transplant. Heart transplant continues to be considered a preferential treatment option, and current trials of VADs as destination devices are directed toward patients who are not considered candidates for transplant. Definition of this population is rendered difficult by the moving target of transplant contraindications and the potential for VADs to reverse certain contraindications. A case in point is the contraindication based on “irreversible” pulmonary hypertension. A recent HFSA workshop focused on this issue and will yield recommendations for relevant diagnostic criteria. However, it should be recognized that criteria for irreversibility of pulmonary hypertension are controversial. Patients with high and poorly reversible pulmonary arterial pressures and vascular resistance may demonstrate marked improvement with prolonged, aggressive vasodilator therapy or may reverse following a period of VAD support. *A priori* identification of a patient whose pulmonary vascular resistance will improve following VAD implantation is difficult or impossible. As advancements in VAD technology translate into improved reliability and patient acceptance and reduced morbidity, the need to clarify the distinction between candidacy and contraindication for transplant will decrease in importance, and destination VAD trials will seek to enroll patients who would otherwise be candidates for transplant.

REMATCH showed a significant reduction in mortality among patients randomized to receive the VAD, with a point estimate for relative risk of 0.52 (95% confidence interval, 0.34 to 0.78;  $p = 0.001$ ). One-year mortality in this group was approximately 50% (compared with 75% in the medical treatment group). However, mortality in the VAD group was extremely high at 2 years, with recent re-estimates running approximately 70%. Furthermore, this group experienced a high rate of co-morbid events and device failures. Nevertheless, the FDA accepted results of this landmark study as

sufficient evidence for approvability of the Heartmate™ VAD as destination therapy for select patients with severe heart failure.

A post-hoc subset analysis of REMATCH indicated that the population that was receiving intravenous inotropic agents at time of entry contributed numerically more than the remaining population to the survival benefit achieved with VAD therapy. However, it is difficult to determine the degree to which inotropic therapy marked an even sicker population, as opposed to contributing directly to the demise of patients randomized to medical therapy. Furthermore, this analysis did not yield a statistically significant treatment-by-subgroup interaction, and therefore poses a dilemma regarding the justification for restricting approval to those patients who manifested the numerically greater treatment effect (post-hoc).

It is reasonable to conclude from REMATCH that the current generation of VADs provides us with a device applicable to patients who are not transplant candidates and in whom death may be considered imminent—eg, 50% 6-month mortality. The goal of future trials should be to document a risk-benefit profile that will support expanding the applicability of VAD treatment to broader, well-defined populations.

### Trial Design

The optimal means for defining clinical efficacy continues to be the randomized, controlled trial. As difficult as it is to ascertain efficacy based on performance criteria for VADs as bridges, the task is more daunting for VADs as destination devices, particularly when efforts are directed toward expanding the target population beyond one with extremely limited life expectancy (eg,  $\leq$ 6-month median survival). Under the best of circumstances, our ability to predict outcomes within an imputed control group, based on findings in a preceding trial, is limited. As we move toward less-sick populations, heterogeneity of outcome increases, and establishing an anticipated survival rate, against which outcomes of patients receiving a new VAD may be measured, becomes exceptionally difficult.

Where a technical modification within a VAD (to be employed for destination therapy) is considered unlikely to alter efficacy, then approval may be achievable through bench testing and/or uncontrolled clinical trials, matching safety against identifiable standards. However, with new devices, or more major modifications of existing devices, given the above considerations, uncontrolled clinical trials matching outcomes to performance criteria established within previously investigated populations are unlikely to yield convincing support for clinical efficacy.

For extremely sick populations, such as those enrolled in REMATCH (see population considerations, above), randomization between device and medical therapy is likely unachievable. Therefore, trials in such populations are best performed with randomized comparison against existing devices. Consideration must then be given to the degree of

confidence required to rule out inferiority of the test device to the comparator.

For example, for a control device that is associated with a one-year mortality rate of 50% in a given population, a sample size of approximately 78 patients per arm would yield 80% power to exclude a 20% absolute increase in annual mortality (from 50% to 70%) with use of the experimental device, with one-sided  $\alpha = 0.05$ . Smaller differences in absolute mortality could be ruled out by an increase in sample size. There would be little value in a study that merely ruled out an even larger survival decrement. Furthermore, with sequential active comparator trials, each trial introduces further uncertainty regarding non-inferiority relative to the originally documented event rate. Where such a large possible increment in mortality is accepted, it is important to emphasize the need for post-market surveillance.

The sample sizes required within active comparator trials employing mortality as the primary endpoint have been considered prohibitive by some device manufacturers. The situation may be improved by the use of multiple or composite endpoints (see below). For example, smaller sample sizes may be sufficient to demonstrate non-inferiority with regard to an endpoint of combined mortality and morbidity, or endpoint strategies that incorporate functional status or health status as well as morbid events. Furthermore, if a device were to demonstrate significant superiority with regard to non-fatal morbid events and/or functional status, it may be possible to infer a low *clinical* likelihood of survival inferiority. Under such circumstances, there may be willingness to tolerate greater *statistical* uncertainty regarding the possibility of inferiority in survival.

As VADs improve to the point of justifying investigating less-sick populations, it will likely be impossible to estimate the impact of VAD therapy on morbidity and mortality in such populations based on comparison to historical or non-randomized controls. Initial evaluation of the efficacy and safety of VADs within less-sick populations will require prospective randomization to optimal medical therapy. The feasibility and acceptability of such trials will be enhanced by explicitly allowing “rescue” VAD implantation for patients later reaching a clinical profile of severity such that subsequent mortality is highly likely with medical therapy alone. Definition of optimal medical therapy within such trials is presently under consideration by a working group of the HFSA.

Following approval of a VAD, systematic post-market surveillance is essential. Deployment of VADs more broadly beyond the confines of a clinical trial will result in increased variability in patient selection, technical proficiency, and medical management, factors that will impact importantly on clinical outcomes. CMS has instituted strict criteria for sites approved for coverage for the Heartmate™ as a destination device. These criteria include approval of the center as a transplantation center and performance of at least 15 VADs as bridge to transplantation from January 1, 2001 through September 30, 2003. In addition, the center must

be a member of a “national, audited registry that requires submission of health data on all VAD destination therapy.”

### Endpoints: Efficacy

Mortality will always remain a principal endpoint of interest. For any new device or modification of an existing device, there must be assurance that the differences from existing technology do not impart a decrement in survival, beyond an acceptable level of tolerance. If such assurance cannot be derived from reasonable assumptions regarding the impact of a revised or novel design, or from bench testing, then it must be derived from clinical investigation. (See design considerations, above.) For deployment of VADs in broader populations than previously explored, the effect on mortality compared with medical therapy alone must be estimated *de novo*. It is possible for future device approvals to be based primarily on alternative or composite endpoints (see below). However, interpretation of the relevance of such results will always require a reasonable point estimate for survival.

Need for hospitalization has become a standard endpoint in heart failure clinical trials,<sup>29,70,71</sup> because of 1) its implication regarding disease activity or progression, 2) its detracting from a favorable H-QOL, 3) its role as the principal contributor to overall health resource utilization, and 4) its correlation with mortality. Hospital utilization may be measured in terms of time to event (hospitalization or re-hospitalization), total number of events, or total days. Hospitalization rates must be explored in conjunction with mortality, since an intervention that increases mortality reduces the potential for hospitalization. Such exploration may be performed through an analysis of 1) time to death or hospitalization or 2) total numbers of hospitalizations or hospital days corrected for follow-up time alive (or, conversely, by counting days alive, out of hospital). For non-fatal events, such as hospitalization, the latter approach offers the advantage over time-to-first event analyses of not over-valuing the initial event while censoring all subsequent events.

Analysis of cause-specific hospitalization—ie, due to, or associated with, worsening heart failure—offers the advantage of focusing on events that are most likely to be influenced by VAD treatment and, therefore, yielding larger effect sizes. Since all hospitalizations are important to the patient and all are important in considering total health care utilization, an argument may be made in favor of all-cause hospitalization (together with deaths). In particular, hospitalizations due to infection, thrombosis, hemorrhage, device malfunction, and other device-related complications, must be considered in exploring hospitalizations as an endpoint. A reasonable approach is to incorporate cause-specific (eg, heart failure-related) hospitalization into the primary efficacy endpoint and to secondarily examine all-cause hospitalizations to assure that safety limitations do not offset the gain derived from heart failure-related efficacy.

Beyond outcome events, such as death and hospitalization, efficacy may be demonstrated based on measures of functional capacity, symptoms, and H-QOL. In fact, it is

important to assure that reductions in mortality and/or hospitalization rates with a particular VAD are not associated with an unacceptable decrement in functional status. Results based on maximal or submaximal exercise testing and on health status instruments both represent potentially acceptable efficacy endpoints. Existing H-QOL instruments have sufficient evidence for validity, reproducibility, sensitivity to clinical change, and predictive value to justify incorporation into primary efficacy analyses for VADs.

There is justifiable concern regarding potential bias that may be introduced into H-QOL results within unblinded trials. A number of design factors should be implemented to mitigate against such bias: 1) use of a patient-driven instrument; 2) administration of the instrument by, preferably, a blinded observer or, minimally, one not involved in direct care of the patient; and 3) demonstration of concordance with other physiologic and/or clinical endpoints.

Composite endpoints may be invaluable in improving the power of a clinical trial and reducing sample-size requirements. Use of composites is particularly justifiable when the components have a mechanistic connection and/or correlation. Under these circumstances, a significant overall effect may result from trends toward benefit within each component. Multiple endpoints may be aggregated either through development of a composite score or by alpha adjustment of the components' results. Overall positivity may be inferred from a single positive component, but with a *p*-value adjusted for multiple comparisons; or by requiring at least one significant component ( $p < 0.05$ ) and a positive trend ( $p > 0.05$ ) for one or more other components.

Combining survival with health status represents a promising direction for exploration. The endpoint of “neurologically acceptable” survival may be useful in incorporating the clinical relevance of permanent, serious adverse neurologic events into the efficacy analysis. Additionally, survival may be combined with H-QOL (quality adjustment of survival time). Exploration of such an endpoint has the potential for highlighting efficacy for a device that confers equivalent survival, but incremental improvement in health status, compared with a previously approved device. At present, constructing such endpoints poses challenges, since heart failure-specific H-QOL instruments are not specifically designed to capture the impact of neurologic and other non-heart failure VAD complications on health status. Methods for combining these various factors into a single measure may require further validation.

Beyond endpoints of direct clinical relevance to the patient, endpoints related to ventricular remodeling (in conjunction with clinical endpoints) may become worthy of consideration for trials of future VADs or other devices that may benefit cardiac structure and/or function (“bridge to recovery”). There has been remarkable concordance between drug effects on parameters of ventricular remodeling, particularly ventricular volume, and on subsequent clinical outcome.<sup>72</sup> There is increasing evidence that VADs and other mechanical devices have the potential to reverse or prevent adverse ventricular remodeling and, in the case of future

VADs, may justify temporary implantation, followed by removal.<sup>73-6</sup> Given the established importance of ventricular remodeling in the pathogenesis of heart failure and its strong correlation with patient outcomes within clinical trials, it is justifiable to consider incorporation of remodeling-related endpoints, in conjunction with more clinically-related endpoints, into evaluations of efficacy for devices deployed for bridge-to-recovery.

### Endpoints: Safety

The present generation of VADs carries substantial safety concerns, particularly infection, thrombotic events, neurologic events and/or impairment, and hemorrhage. (See section on VADs as bridge to transplant). Interpretation of efficacy results requires an assessment of the risk-to-benefit ratio. Safety standards must be pre-specified, based on individual and/or aggregated rates of these serious adverse events. One approach to assist in the risk-to-benefit analysis entails creating a single composite of heart failure-related events combined with device-related serious adverse events. For example, one can examine freedom from death, heart failure hospitalization, and stroke.

### Summary

A wide array of novel medical devices on the horizon offers promise of substantial clinical benefit to patients with heart failure, including those presently considered to be "end-stage." VADs are an established tool for allowing critically ill patients to undergo cardiac transplant. We have witnessed the first definitive demonstration of survival benefit from VADs as destination devices. Novel advances in VAD design hold the potential for expanding the indication to broader populations and offering improved survival, H-QOL, and device reliability, and/or reduced device-related morbidity. The challenge will be to design clinical trials that will expedite advances in the field, while assuring the safety and efficacy of new devices. Such designs will facilitate the application of new devices as bridges to transplant, as destination therapy, and as instruments for improvement in underlying cardiac pathology.

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## Appendix 1

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