Testimony on Behalf of the International Society for Heart and Lung Transplantation (ISHLT)

To the

Medicare Coverage Advisory Committee (MCAC)

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Left Ventricular Assist Devices (LVAD) for Destination Therapy

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Mario C. Deng, MD

REMATCH has provided the proof of principle for the benefit of chronic MCSD therapy. Over the last two decades, mechanical circulatory support devices (MCSD) have been developed at a rapid pace with the goal of supporting patients with advanced heart failure as a bridge to cardiac transplantation (BTT) and a bridge to recovery (BTR). More recently, based on the results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study, MCSD therapy has become available as permanent or destination therapy for a restricted population of advanced heart failure (AHF) patients not felt to be appropriate candidates for transplantation. The REMATCH trial was a landmark study demonstrating the benefit of MCSD in nontransplant-eligible AHF patients. MCSD-supported patients had significantly better survival at 1 and 2 years when compared to advanced endstage heart failure patients treated medically (many with chronic parenteral inotropes). Although a survival benefit was clear, it was over a 2-year time period only and morbidity was substantial, particularly with respect to infections, neurological events, and pump malfunctions.

Translation of REMATCH results into clinical practice is challenging. Following publication of the REMATCH results, the Food and Drug Administration (FDA) approved the Heartmate MCSD for destination therapy on Nov 05, 2002. Based on previous

experience, two post-FDA approval trends are likely: first, centers will begin to place these devices into patients with a less dismal prognosis than those randomized in REMATCH; and second, the expansion of centers will lead to the establishment of startup MCSD programs a) having less experience than established chronic MCSD centers, and b) providing no onsite heart transplantation capabilities. These trends may decrease the survival benefit from destination MCSD therapy. There may, in the worst case scenario, no longer be a detectable survival benefit in post-approval chronic MCSD implant practice, implying that destination MCSD therapy only results in a switch of the mode of death. Instead of dying from refractory heart failure, transplant-ineligible AHF patients receiving mechanical support would die instead from infection, coagulopathies, neurological events, or catastrophic device malfunction. ***Although the observations of 129 patients in the REMATCH trial provided definitive evidence of benefit for this specific population, they can neither adequately identify subsequent target populations nor define centers in which the next phase of implementation should occur.*** The immediate risks of uncritical generalization of REMATCH results may be device implantation into patients who are less likely to benefit. Viewing this potential development within a social science perspective, it is important to avoid “repeating history”. We have to bear in mind the problems that led to a moratorium on cardiac transplantation in the 1970's and of artificial heart implantation in the 1980's after an initial series of implantations of the Jarvik-7 total artificial heart.

This challenge must be met by a collaborative strategy focusing on safety and efficacy. In suggesting policies for identification of centers to qualify for chronic MCSD implantation, our over-riding commitment is to the protection and benefit of the individual patient. A major concern is the inappropriate application of MCSD for patients who are “too well” (thus needlessly subjected to an expensive and unproven long-term therapy) or “too ill”

(with multisystem dysfunction and a low probability of successful outcome) if decisions for implantation are made by individuals or institutions not truly experienced and expert in the allocation of therapies for advanced heart failure. In order to ensure safe and effective destination MCSD services, a systematic strategy should be developed including 1) documentation of all destination MCSD implants in an appropriate database to facilitate risk factor identification and development of predictive models, 2) translational research on the impact of MCSD on innate and adaptive immune responses, infection, coagulopathies, neurological dysfunction, and nutritional status, 3) expeditious and coordinated improvement of management practices, 4) development of reimbursement rules and center standards for hospitals desiring to perform chronic MCSD therapy by payors such as the Centers for Medicare and Medicaid Services (CMS) in the U.S.. Given the multidimensional challenge of the post-REMATCH era, a continuous collaborative strategy is in the best long-term interest of MCSD centers, manufacturers, regulatory agencies and payors/insurers.

ISHLT recommends criteria-based identification of appropriate chronic MCSD-centers. Different options exist to identify appropriate chronic MCSD centers. The options are outlined in the ISHLT-document, *Destination Mechanical Circulatory Support – Proposal for Clinical Standards***,** which has been provided to the MCAC as part of our written testimony and has been peer-reviewed and approved for publication in the April 2003 issue of the Journal of Heart and Lung Transplantation. The option recommended by the ISHLT Board of Directors is as follows:

Option V*: Enforce fulfillment of a minimum set of established requirements for physicians, surgeons, personnel, training, and infrastructure prior to initiation of chronic MCSD programs in all interested centers, with assessment of center-specific outcomes on an annual basis and continued approval based upon achievement of target outcomes.* **Rationale**:

Fulfillment of a set of minimum requirements, as defined below, will maximize the likelihood of satisfactory performance and outcomes, thus safeguarding the individual patient, while at the same time maintaining the balance of dissemination of the new therapy for the benefit of the large AHF population not eligible for heart transplantation.

Therefore, ISHLT proposes the following minimum set of requirements for chronic MCSD centers:

- Established heart failure program directed by ***specialized heart failure cardiologists*** who have extensive experience in advanced heart failure medical therapy, the care of patients following heart transplantation, and the care of patients receiving mechanical circulatory support as a bridge to transplantation with a potentially chronic MCSD. At least one heart failure cardiologist at the MCSD center must have expertise in management of all of these modalities as well as appropriate allocation of specific therapies to individual patients as determined by severity of heart failure and response to alternative therapies. His/her experience must have been obtained at a heart failure, transplant, and MCSD-bridging center in which he/she had personal experience caring for 10 or more patients on MCSD support, including out-of-hospital care, with device types with the potential for chronic (>2 months) support and patient ambulation. .
- ***Established surgeons*** at the MCSD center who are personally experienced and expert at the implantation and management of MCSD. At least one surgeon at the MCSD center must have experience at a heart transplant, heart failure, MCSD-bridging center and have documented expertise at implantation, peri-operative and post-operative management and removal of such devices. Her/his experience must include implantation as the primary implanting surgeon of at least 10 mechanical circulatory support devices which have the potential for chronic (>2 months) support and patient ambulation.

- ***Adequate training*** for other participating physician, surgeon, and non physician staff and faculty through educational fellowships and programs conducted at an established chronic or bridge-to-transplant MCSD center.
- ***Established infrastructure*** for infectious disease management, post MCSD nursing and post MCSD social work, with written protocols for pre/intra/post operative MCSD management including end of life situations.
- Center reporting of chronic mechanical support program ***implant volumes and outcomes*** at 1 month, 6 months, and 12 months, which meet or exceed previously established target volumes and outcomes for all such programs.
- Quality Assurance Program within the MCSD center, including ***participation in the ISHLT MCSD Database***.
- AHF-related ***research and teaching*** program.

The ISHLT MCSD Database is an answer to the challenge using continuous outcome evaluation. To achieve a continuous mechanism of high quality outcome data, a multidisciplinary conference in June 2000 jointly sponsored by the American College of Cardiology and a number of major national and international medical and surgical societies brought together physicians, scientists, the US Food and Drug Administration (FDA), and industry representatives to discuss the future role of MCSD and to establish consensus on design principles of future MCSD research. In this conference, a broad consensus was reached that there should be a mandatory database for all implantable MCSD. Therefore, the International Society for Heart and Lung Transplantation (ISHLT), which had, soon after its inception in 1981, initiated the highly successful Heart and Lung Transplantation Registry, developed the international MCSD Database. United Network for Organ Sharing-

Transplantation Informatics Institute (UNOS-TII) in Richmond, VA, was awarded the contract to run this database. Based on the long-term goals of the ISHLT MCSD Database, the following design items seemed essential for the new MCSD Database:

- The ISHLT MCSD Database should reflect overall ***current practice patterns, not just the practice of selected centers of excellence*** because those results could not be generalized to the average center and the average patient in US- and non-US centers. To capture all MCSD implants worldwide, the database should be mandatory and not a voluntary registry
- The ISHLT MCSD Database should enable evaluation of ***patient safety*** with all current and future MCSD designed and capable of supporting the circulation for >30 days. This should, for the first time ever, be accomplished by ***applying uniform consensus definitions of complications to all devices and thus providing a framework for measuring every device along the same set of critieria***.
- The ISHLT MCSD Database should enable evaluation of ***MCSD efficacy***, as defined by gain of survival though MCSD-intervention in relation to preimplantation risk of dying from heart failure. This goal should be, for the first time ever, accomplished by ***integrating validated heart failure risk prediction parameters in the preimplantation assessment form***.

Specific aims and mechanisms of the ISHLT MCSD Database. From the scientific point of view, the purposes of the MCSD Database are to capture worldwide data relating to the implantation and outcome of patients receiving cardiac assist devices designed for and capable of use for 30 or more days, to identify risk factors for complications, to generate predictive models of outcome for given patient profiles, to improve patient selection and

management before and after device implantation, to generate statistical analyses of the data that can be used as the underlying evidence/justification for government agency funded studies and clinical trials and to identify overall and best practices with the aim of improving current practices. The database consists of three tiers of data. Tier 1 includes basic data that focus on the specifics of the device type, surgical implant procedure and indications for implant, as well as outcome. Tier 2 data includes details regarding the specific patient-related complications and events subsequent to device implantation. Tier 3 consists of device-related events compatible with FDA postmarketing surveillance requirements. This data will be invaluable as it will be collected at the source by the clinicians using the devices and should reflect an unbiased assessment of what took place. Data such as this will be sought out by a number of clinicians and specialties. All centers worldwide known to perform MCSD implantation have received the invitation to participate in the MCSD data collection process in December 2001. In February 2002, ISHLT launched web-based Tier 1 data collection, and it is anticipated that Tier 2 and 3 data collection will start in 2003.

The ISHLT-MCSD Database as an ongoing continuous collaborative effort. The challenge for continuous databases such as the ISHLT MCSD Database is a well-defined consensus among participating societal groups, specifically professional experts, regulatory agencies such as the FDA, payors such as CMS, and industry. These groups present with complementary, occasionally conflicting interests. The combined effort of the various stakeholders is required to address issues of goals, data format and management, funding. compliance, and access. The responsibility to support such a Dabatase should be shared between surgical and medical expert societies representing the physicians involved in using these devices, industry, payors, and governmental agencies. For example, the legitimate interest of payors in the MCSD Database includes financing of evidence-based medicine

while avoiding payment for interventions which have not been demonstrated to be safe and effective, and, thus, are not in the best interest of their customers. Payors would clearly not want to pay for a mode switch of death. The currently best, and probably only, way of ensuring the efficacy of chronic MCSD therapy is by utilizing a mechanism such as the ISHLT MCSD Database. The MCSD Database is operated by the ISHLT, rendering the foundation and mechanics of the Database least susceptible to criticism of industry bias. Furthermore, ***the ISHLT-MCSD Database is fully operational and has been ongoing for one year at the time of this testimony. This is specifically valuable in light of the recently completed REMATCH trial***.

Summary and perspectives. We envision that centers currently performing bridge-to-transplant MCSD implantation in the setting of an established advanced heart failure and heart transplant program would likely be able to meet chronic MCSD-center requirements immediately. Similarly, cardiologists and cardiac surgeons experienced in MCSD surgery as well as transplantation and advanced heart failure therapy who have relocated to a non-transplant heart failure center would likely justify inclusion of their new center as a MCSD center if the appropriate infrastructure and personnel training were in place. If MCSD destination therapy is deemed efficacious for a sufficiently large subset of advanced heart failure patients, additional centers wishing to provide this therapy could qualify by fulfilling the above requirements through the acquisition of appropriate surgical and cardiological personnel or through appropriate training. In this context, it is our recommendation that ***funding for these procedures only be provided to facilities meeting MCSD center criteria as outlined above including participation in the mandatory MCSD-database (similar to the mechanism of reporting transplantation to UNOS)*** and that these payments be adequate to meet reasonable cost requirements. To generate ongoing scientific evidence on MCSD safety

and efficacy, ISHLT believes that a mandatory and uniform database incorporates the interests of all participating groups. ***Only the rigorous analysis of accurately collected outcome data for a variety of MCSD can ultimately provide the individual patient with the best choice of support for long-term quality and duration of life***. The care, commitment, and accuracy of the data collected by each participating institution will determine the safety and efficacy of chronic MCSD as a new treatment option for one of the most difficult and costly medical problems—the malignant syndrome of advanced heart failure.

Mario C. Deng MD
Medical Director, ISHLT MCSD Database
Columbia University
Phone +1-212-305-0200
Fax +1-212-305-7439
Email md785@columbia.edu