

PROPOSED DECISION MEMO FOR VENTRICULAR ASSIST DEVICE FOR BRIDGE-TO-TRANSPLANT AND DESTINATION THERAPY (CAG-00432R)

Commenter: INTERMACS Executive Committee

Organization: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

Date: August 29, 2013

Comment:

INTERMACS appreciates the opportunity to respond to the proposed CMS decision memo for Ventricular Assist Devices for Bridge-to-Transplant and Destination Therapy (CAG-00432R) which would remove the requirement for hospitals implanting durable mechanical circulatory support (MCS) devices to report data to INTERMACS. CMS has recognized the value of INTERMACS in the past as a repository of data and the source of analyses that are unavailable from other sources. We disagree with the decision to eliminate the requirement for mandated participation in a national registry, such as INTERMACS. Our response will detail the many important benefits that INTERMACS provides relevant to issues of coverage, quality assurance, and patient safety. Over the past 6 years, INTERMACS has collected and analyzed data which:

- Facilitate comparison of individual hospital outcomes to an aggregate of national device data.
- Allow comparison of Medicare-age population data with non-Medicare patients.
- Provide individual hospital quality assurance information through INTERMACS quarterly reports.
- Identify and refine patient populations which are most likely to benefit from chronic device therapy.
- Quantify markers of poor outcome that have led to change in practice patterns.
- Provide data that injects aggregate perspective against which single or several institutional experiences can be compared, particularly related to device safety issues.
- Allow truly longitudinal data (5-10 years or more) collection and analysis in the domain of intended permanent (destination therapy) use of durable devices.
- Track emerging experiences with new devices in the “real world” of clinical practice for extended intervals that are beyond the scope of clinical trials and post-market studies, and that are important for evaluation of long-term safety and efficacy.
- Provide risk-adjusted expectations of outcomes at individual centers based on multivariable risk models of a national aggregate of MCS patients, facilitating fair comparisons of hospital performance with other centers.
- Provide the FDA with important data on safety that complement pre- and post-market studies.
- Provide a template to Industry for data collection in pre- and post-market studies.
- Examine longitudinal quality of life and functional outcomes with device therapy which will provide critical information to patients and providers who are considering this treatment option.

Regarding:

“Facilities must track patient outcomes including survival, adverse events (e.g. bleeding, infection, stroke, and device malfunction), functional status, and quality of life in a way that allows comparisons with other institutions and facilitates internal quality monitoring and improvement.”

We agree that individual facilities must track their outcomes, but simply comparing their results to other institutions without a national audited well-populated database will miss important data that are relevant to coverage decisions.

- National aggregate risk adjusted data that would generate “expected” outcomes at individual hospitals are only possible with a comprehensive national database such as INTERMACS. Such “observed to expected” (O/E) outcomes could form a portion of the reimbursement algorithms.
- The “pay for performance” concept in healthcare reimbursement will almost certainly target quality in terms of metrics like survival, freedom from adverse events, and length of stay. A comprehensive registry such as INTERMACS is the most logical way to determine standards based on national data that could include all payers rather than just the Medicare population.^{9,10} Such analyses would provide valuable insight into whether outcomes in non-Medicare beneficiaries differs from Medicare beneficiaries.¹ **(Figure A)**

Figure A

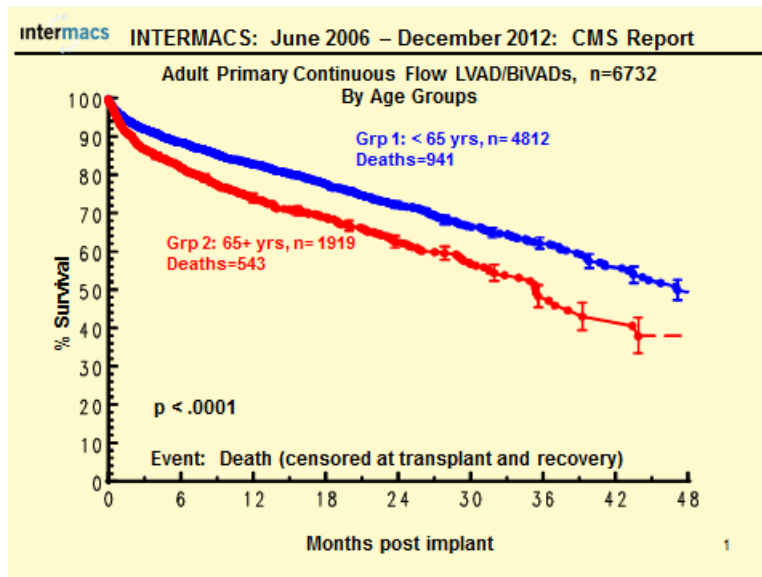


Figure A. Kaplan-Meier depiction of survival following implantation of a continuous flow ventricular assist device, stratified by age at implant. Group 2, the Medicare age population, has significantly worse survival than the younger group ($p < .0001$). LVAD, left ventricular assist device; BiVAD, biventricular assist device.¹

- Data supplied from INTERMACS to CMS indicated that no detectable differences in mortality currently exist between hospitals based on implant volume. The care exercised by VAD teams in selecting patients for device implant currently exists in an environment of mandated submission

of outcomes data through INTERMACS. Quarterly INTERMACS reports provided to individual institutions show their survival outcomes compared to aggregate data from most U.S. VAD hospitals.² (Figure B) In the absence of such surveillance through a national audited well-populated database, VAD teams with small volumes may experience pressures to implant durable VADs in patients with more co-morbidities, who are less likely to survive and benefit, thus driving up healthcare costs.

Figure B

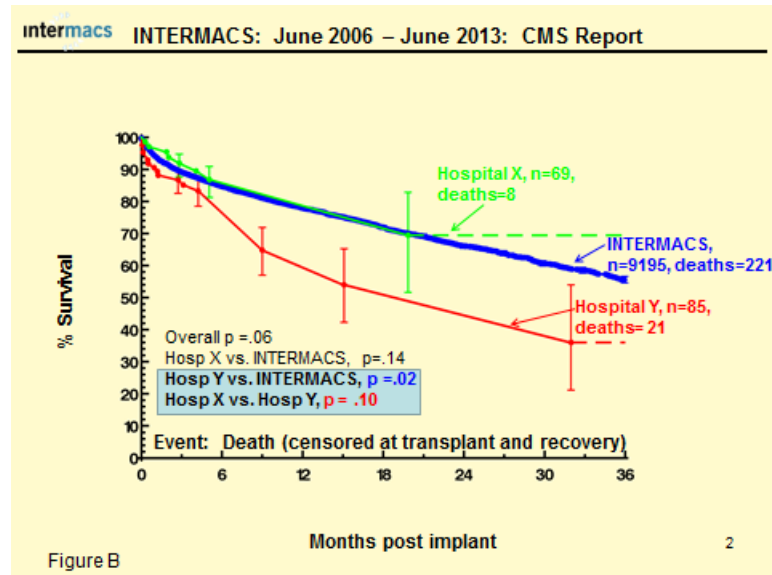


Figure B. Kaplan-Meier depiction of survival after adult primary implant. The blue curve represents the entire INTERMACS experience. The red curve represents a hospital with a survival rate that is significantly below that of INTERMACS. The green curve represents a hospital with good survival but not significantly above INTERMACS. The small number of implants in each hospital, prevents the detection of a significant difference between the hospitals.²

Regarding:

“The evidence is sufficient to conclude that continuing required participation in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) will not adequately address the outstanding evidentiary questions for VADs; therefore, INTERMACS participation is no longer required for VADs to be determined reasonable and necessary and CMS proposes to remove this requirement.”

We respectfully disagree with this statement and cite below several examples of important evidentiary questions which could be answered through a well-managed national database such as INTERMACS:

- The refinement of patient subsets most likely to benefit from MCS therapy can only be accomplished in a reasonable time frame through a mandated national database like INTERMACS.¹¹ An example of such a refinement was the identification of a major increase in early mortality when implanting durable devices in patients in cardiogenic shock (INTERMACS level 1) (Figure C), in which the relative risk of INTERMACS Level 1 was 1.59 (p=.02).³ The dissemination of this information from INTERMACS led to a change in physician practice over

about 2 years, resulting in a progressive decrease in the proportion of durable VAD patients who receive devices while in cardiogenic shock⁴ (Figure D). A national database has the capability to identify other markers of poor outcomes in a more timely and complete manner than reports from individual centers. Avoidance of implantation in patients with poor expected outcomes has likely improved the cost-effectiveness of this expensive therapy.

Figure C

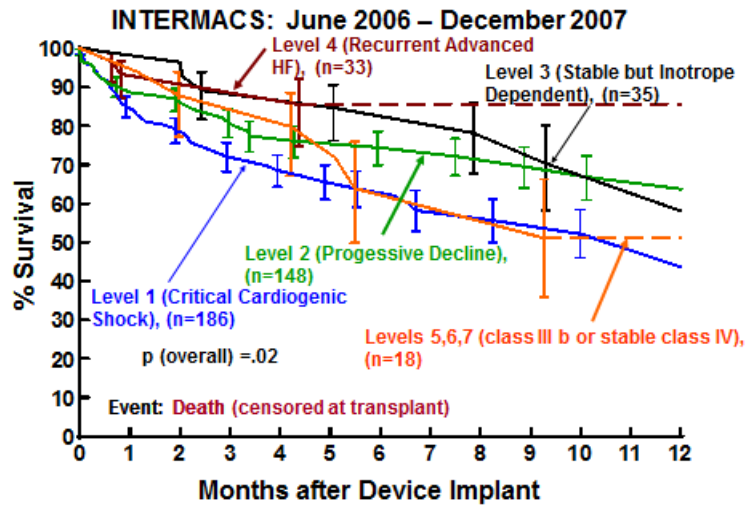


Figure C. Kaplan-Meier depiction of survival after primary implant. The stratification is based on the INTERMACS Patient Profile prior to implant. Note the decreased early survival in Profile 1 (critical cardiogenic shock).³

Figure D

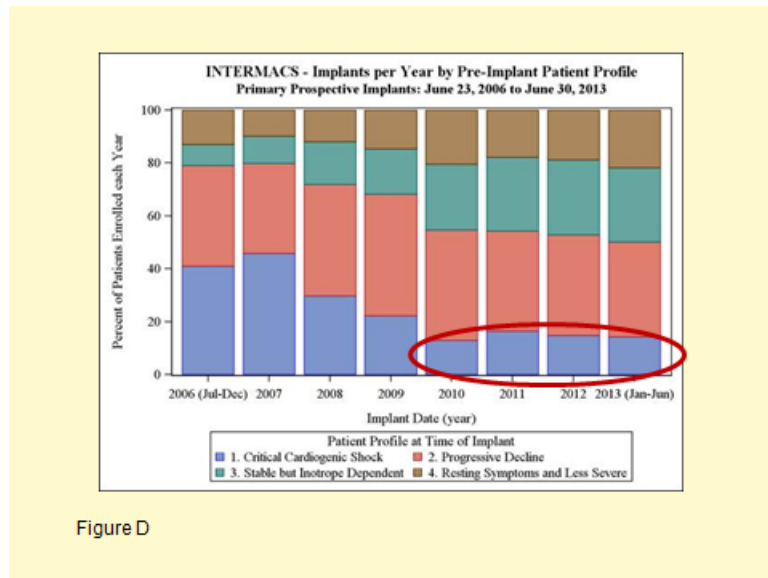


Figure D

Figure D. The distribution of INTERMACS Patient Profiles according to year of implant. Note the decreased proportion of patients in Profile 1 (critical cardiogenic shock) in blue, beginning in 2010.⁴

- Given that follow-up of patients with the HeartMate II continuous flow pump as Destination Therapy is only now exceeding 3 years, and the HeartWare LVAD has just under one year of follow-up as approved Bridge-to-Transplant therapy, termination now of mandated data collection through a national registry would seriously compromise a critically important opportunity to collect longer-term outcomes data on more than just one continuous flow pump. Important differences in performance between these and future pumps is likely, but accurately quantifying such differences will be seriously compromised without accurate national registry data.⁴ **(Figure E)** Such longer term follow-up data could provide important information to guide coverage decisions for specific classes of emerging devices.

Figure E

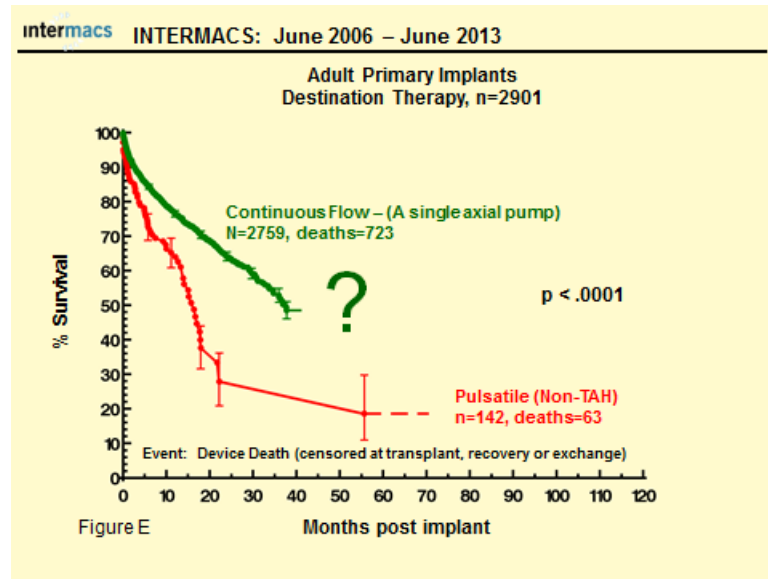


Figure E. Kaplan-Meier depiction of survival after adult primary implant in patients with an initial strategy of destination therapy. The experience with continuous flow pumps is limited (the single continuous flow pump was approved for DT therapy in January, 2010).⁴

- Informed patient decisions require detailed knowledge about outcomes that extend beyond the strict selection criteria and truncated follow-up of clinical trials. Although LVADs are currently approved for INTERMACS level 4 patients and some level 5 patients, fewer than 1 in 5 patients implanted have been on oral therapy at home, so ongoing results in this ambulatory population will be critical to track.¹⁵ When death is less imminent than for the INTERMACS profiles 1-3, decision-making for patients and families becomes increasingly more complex, as emphasized in the AHA Scientific Statement on Decision-Making in Advanced Heart Disease¹⁴, which also states that the choice to undergo a lifetime of mechanical circulatory support “represents one of the most difficult decisions that patients and clinicians can make”. The increasing national focus on individual patient-centered care and shared decision-making requires the type of detail, relevance and balance that can only be derived from a living registry of unselected contemporary data across sites.

- The ability of CMS to rely on the FDA for comparative data between devices or device types would be severely impaired without mandated participation in a national registry, such as INTERMACS, to collect a large sample of such devices. The FDA has embraced the value of INTERMACS to provide device and patient data during post-market studies, which could affect future coverage decisions.^{8, 13}
- The unpredictable nature of translating expected performance of one pump to others (which may have direct relevance to longer term coverage decisions), or even to past performance of the same device, is illustrated by the identification of a 3% increase in actuarial incidence of pump replacement for suspected pump thrombosis in the HeartMate II device during 2011 and 2012.⁵ **(Figure F.1)** Were it not for a comprehensive analysis of the national experience by INTERMACS, individual center anecdotes might have fueled a major shift away from device use for patients whose only real chance for survival was a device implant. Only INTERMACS could provide an appropriate credible analysis of a large national database that indicated a significant but limited magnitude increase in the risk of thrombosis and pump exchange. Of major importance, there was no decrement in survival in the more recent era **(Figure F.2)**, consistent with a demonstrated overall improvement in 6 month survival of between 86% and 87% in the post market commercial era versus 75% six month survival observed during the HeartMate II pivotal clinical trial.^{16, 17} These data from INTERMACS appropriately informed and enabled the DSMB for the REVIVE-IT (Randomized Evaluation of VAD Intervention Before Inotrope Therapy) Trial to reasonably conclude that the trial should continue.

Figure F.1

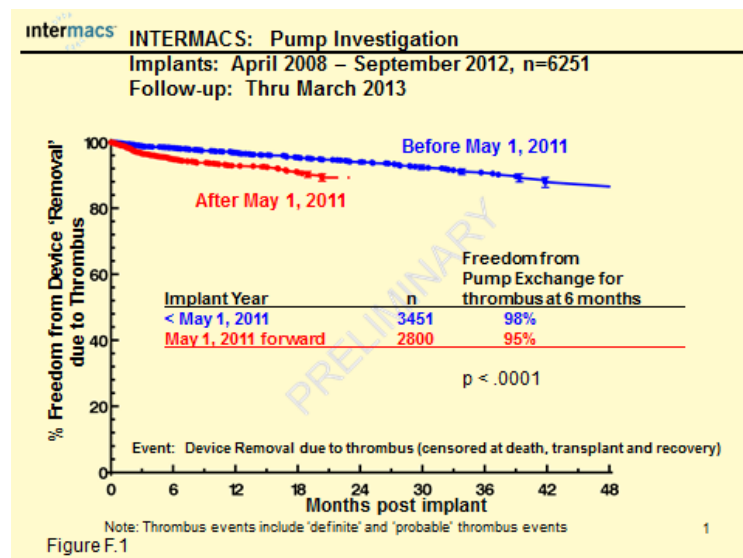


Figure F.1. Stratified actuarial curves depicting freedom from HeartMate II pump exchange attributable to pump thrombosis. Note the significant increase in events after May, 2011, but the magnitude of increase was relatively small.⁵

Figure F.2

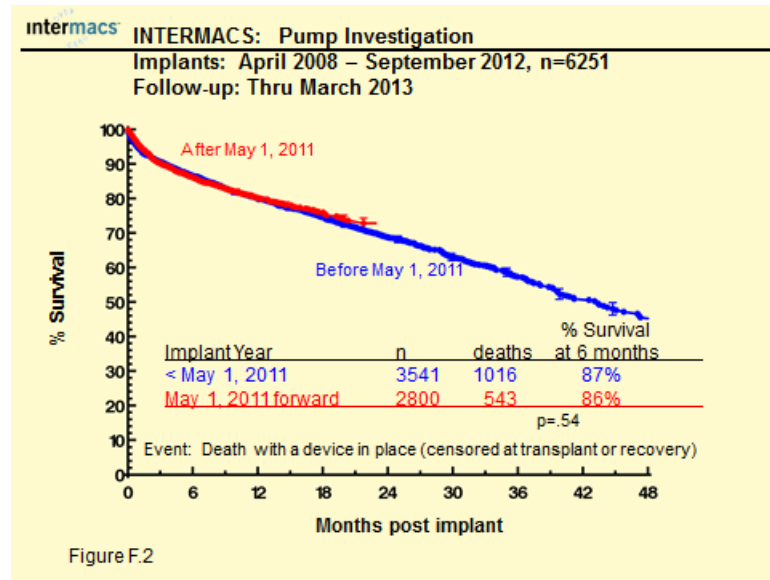


Figure F.2. Stratified actuarial curves depicting survival in patients receiving a HeartMate II pump. Notice the essentially identical survival in the two cohorts.

- The example cited above underscores the uncertainty of predicting future performance of current or future pump designs that enter the clinical arena. Subtle changes in pump design, patient selection, and patient management (such as anticoagulation therapy or treatment of right heart failure) require long-term surveillance of a large sample of patients receiving implants in order to identify changes in outcomes that may affect coverage decisions. Because of limited sample size and duration of follow-up, the FDA pre- and post-market studies may not sufficiently monitor potential practice changes which may not become apparent for several years after device approval. For example, the HeartMate II BTT pivotal FDA trial examined 6 month outcomes in 133 patients. Other examples of limited sample size and follow-up are listed in **Table 1**. Of equal importance is avoidance of non evidence-based changes in practice, pump usage, or management strategies, which could emanate from highly publicized anecdotes if data from a respected national database are not available for analysis.

Table 1




Table 1

Clinical Trial	n	Duration/ maximum follow-up
Pre-Market Approval		
Revive-IT	100	2 year follow-up
HeartMate II: BTT	133	1 year follow-up
HeartMate II: DT	200	2 year follow-up
Post Approval		
HeartMate II: BTT	169	1 year follow-up
HeartMate II: DT	247	2 year follow-up

- As new technology enters the MCS field, novel devices that are substantively or completely different from current axial or centrifugal flow pumps may be approved. The risk of certain types of adverse events or manifestations of device malfunctions could potentially increase several years after implantation. In light of limited follow-up that is required for most clinical trials, such trends and risks would be extremely difficult, if not impossible, to detect without mandatory participation in a national audited well-populated database such as INTERMACS. This could have important implications for patient safety.¹²
- Decisions regarding extension of coverage of durable devices to “less sick” patient populations will depend on appropriate clinical trials such as REVIVE-IT. After the REMATCH trial, INTERMACS provided real world data on the application of such devices for long term implantation. Similarly, following the REVIVE-IT trial, analyses of registry data based on clinical experience with a new patient population could refine the investigators’ conclusions. Relying solely on randomized clinical trials (without appropriate analyses from a national database) for extension of suitable patient populations would not only potentially delay the availability of the therapy to patients who may benefit, but would also remove the ability to refine recommendations based on aggregate real world experience.

Regarding:

CMS discussion of institutional tracking of outcomes: “It is important for facilities to continue to track their outcomes in a way that allows comparisons with other institutions to facilitate internal monitoring and quality improvement and to further refine clinical practices”.

We agree that tracking of outcomes is of central importance in assessing the comparative outcomes not only among individual physicians and institutions, but also among devices as well as the patient populations receiving them. Without a national audited well-populated database such as INTERMACS,

the ability to identify institutional competence as distinct from other risk factors for mortality may be compromised.^{2,4} (Figure G) (Table 2)

Figure G

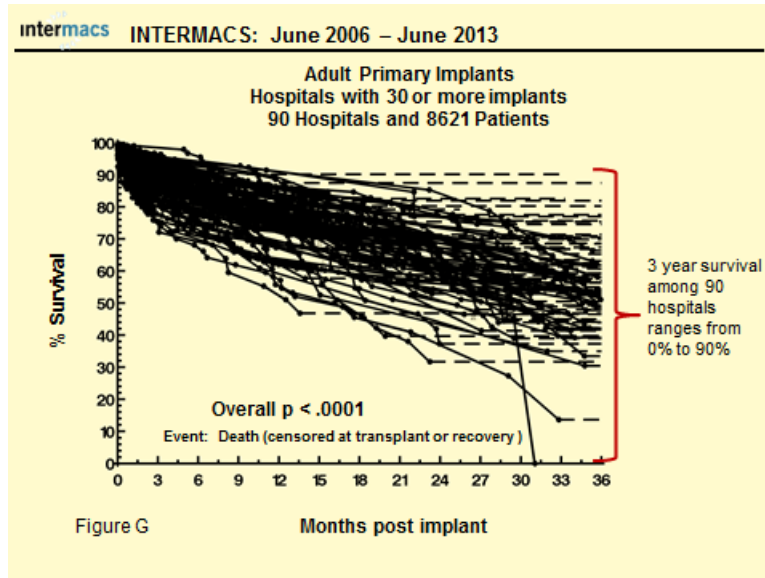


Figure G. Kaplan-Meier depiction of survival after adult primary implant. These depictions are not risk-adjusted. The stratification is based on individual hospitals and only includes hospitals with at least 30 implants. Survival in these hospitals at three years ranges from 0% to 90%.²

Table 2

intermacs Implants: June 2006 – June 2012, Adult Primary Continuous Flow LVADs and BiVADs, DT and BTT, n=5436

Risk Factors for Death	Early hazard		Constant hazard	
	Hazard Ratio	p-value	Hazard Ratio	p-value
Demographics				
Age (older)	1.69	< .0001		
BMI (higher)	1.47	< .0001		
Clinical Status				
Ventilator	1.65	.009		
History of Stroke	1.69	.009		
INTERMACS Level 1	2.45	< .0001		
INTERMACS Level 2	1.89	.0004	1.30	.003
Destination Therapy			1.25	.01
Non-Cardiac Systems				
Diabetes			1.22	.02
Creatinine (higher)			1.10	.008
Dialysis	2.22	.002		
BUN (higher)	1.10	< .0001		
Right Heart Dysfunction				
RVAD in same operation	3.73	< .0001		
Right atrial pressure (higher)	1.36	.002		
Bilirubin (higher)	1.08	< .0001		
Ascites			1.32	.05
Surgical Complexities				
History of cardiac surgery			1.50	< .0001
Concomitant Cardiac Surgery	1.34	.02		

Table 2. Multivariable analysis of risk factors for death after implantation of a continuous flow pump. Applying this risk factor modeling (only available through INTERMACS) to individual hospitals depicted in Figure G could generate risk adjusted “Expected vs. Observed” mortality, which would allow comparison of hospital mortality after taking into account the risk factors in their patient populations.⁴

Regarding:

CMS has acknowledged that: 1) “the procedure, the device and post-operative care will continue to be refined in coming years and it is important to have a means of assessing the quality of patient care over time to ensure that outcomes are maintained or ideally improved. 2) registry data will permit facilities to compare their LVAD experience against that of other implanting facilities to determine the quality of their performance overall as well as to assess whether an individual patient’s care and progress in recovering from the procedure is meeting normative standards”.

The fact that INTERMACS has demonstrated improved survival with a continuous flow device (HeartMate II) over the prior XVE pulsatile device clearly supports the CMS position to continue providing coverage for existing indications. What has not been demonstrated is whether in the real world setting of clinical practice, other devices that have been newly introduced or are yet to enter clinical trials will enjoy the same favorable outcomes. It is well known that data from clinical trials are not always generalizable to clinical practice, which is in part why CMS supported mandated MCS data entry into a national registry. Because of potentially important differences between current and emerging devices in terms of survival, freedom from adverse events, and functional outcome, the strong rationale for continuing data collection, analysis, and quality assessment to evaluate new devices is equally compelling now as it was 10 years ago.

Regarding:

CMS has asserted that “registry data can be an invaluable aid to an implanting facility in ongoing assessment of the quality of care it is providing to its patients”.

INTERMACS agrees with this statement, and we believe that future quality improvement efforts by hospitals will be enhanced by continuing the Quality Assessments provided through INTERMACS. The Quarterly Reports given to each institution provide aggregate national data as well as detailed information about the institution’s own outcomes. **(Table 3)** The overall INTERMACS benchmarks provide metrics against which they can compare and improve their individual performance.² **(Figures H, I, J)** As the number of devices increases and multivariable analyses of the overall database identify risk factors that can increasingly be used to assess risk-adjusted outcomes at each institution **(Table 2)**, the ability to compare institutions and even differing types of devices will be enhanced. With continued maturation of the field and the availability of multiple approved devices, the importance of a national audited well-populated registry as a reference for center as well as device performance in varying patient populations will likely be even more important than today. With possibly different devices being implanted at institutions being compared, a single institutional comparison, without a national registry as a reference, may invoke the metaphor of comparing “apples to oranges”.² **(Figure K)**

Figure H

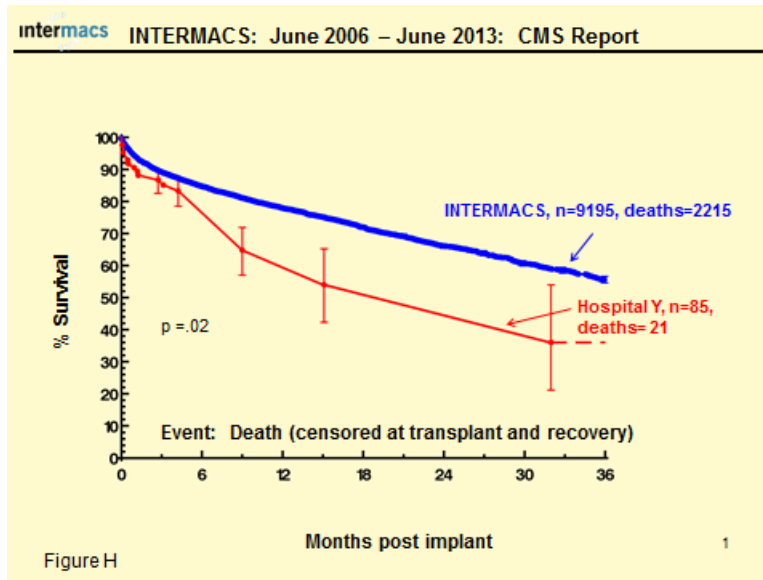


Figure H. Kaplan-Meier depiction of survival after adult primary implant. The blue curve represents the entire INTERMACS experience. The red curve represents the experience of a single hospital. The p-value compares the single hospital with the national experience that is represented by INTERMACS.²

Table 3

Sample of Information Provided Quarterly by INTERMACS

Hospital Comparison to National Benchmarks: Internal Quality Assurance and Improvement

Patient Selection Before VAD
Examples of fields for comparison

	Your Hospital	INTERMACS 2012
% Profile 1		15%
Profile 2		38
Profile3		28
Profile 4		14
Profile 5		3
% Listed / transplant		19%
Likely		23
Moderately		10
Unlikely		3.0
Dest. Therapy		44

Outcomes – Survival (available for each Profile and Intent for comparison to National Outcomes)

	Your Program	INTERMACS National Data* Continuous Flow Only (N=6581 pts)
30 Days		96%
1 year		81% (N=2628)
2 years		70% (N=1001)
3 years		59% (N=252)

Examples of Adverse Event Tracking – Rate per 100 patient months in intervals

	Your Program	Your Program	INTERMACS	INTERMACS
	Per First 100 days	After 100 Days	Per First 100 Days	After 100 Days
Infection			19	5.3
Bleeding			26	1.3
Neuro event			4.1	1.7
Device malfunction			2.5	3.5
Rehospitalization			17	15

Figure I

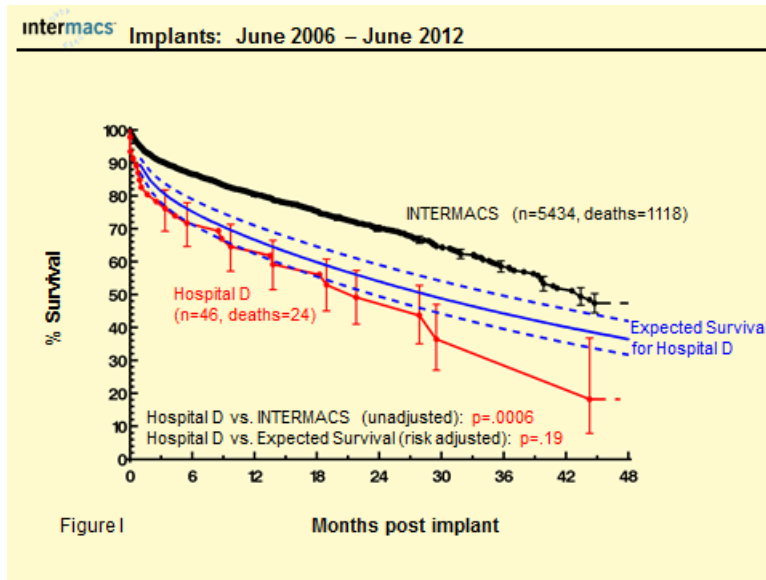


Figure I. This is an example of a risk adjusted assessment of survival for a specific hospital. The red line is the Kaplan-Meier survival depiction for hospital D. The black line is the survival for all patients in INTERMACS. The blue line represents the “expected” survival based on a multivariable risk factor analysis for death (based on the overall INTERMACS population) and is generated by predicting the results at hospital D based on the pre-implant risk factors of the individual patients at hospital D. The comparison (p=.19) provides a risk adjusted evaluation of hospital D.

Figure J

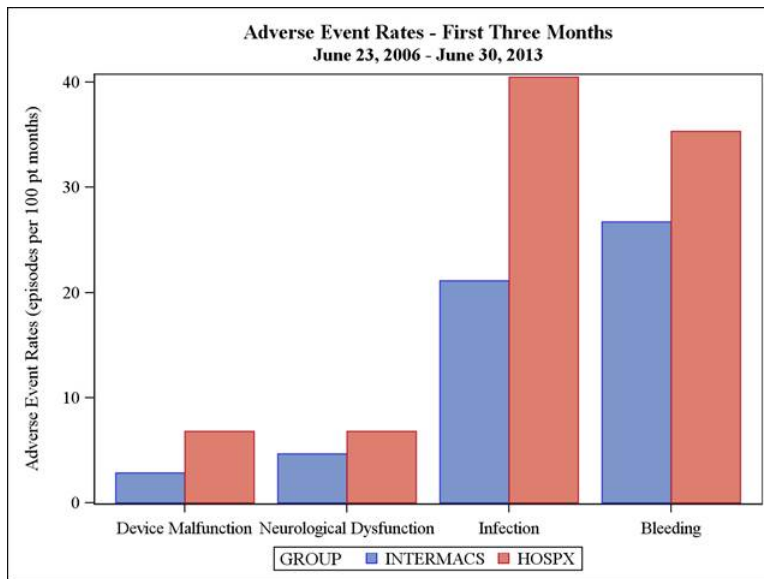


Figure J. Adverse event rates for a single hospital (Hosp X) in red compared to event rates for the overall INTERMACS experience in blue.²

Figure K

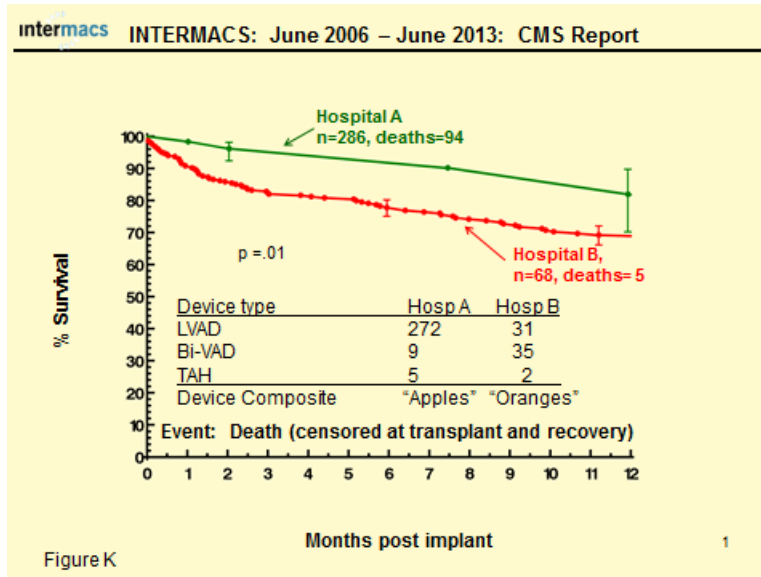


Figure K. Comparison of actuarial survival in 2 hospitals with markedly different device use profiles. Comparing survival at these 2 hospitals without proper risk adjustment for device type as well as patient profiles would equate to comparing “apples and oranges.”²

Regarding:

On Page 40 of the Decision Memo, CMS quoted a paragraph from the publication, “Statement Regarding the Pre and Post Market Assessment of Durable, Implantable Ventricular Assist Devices in the United States”⁷, listing a number of INTERMACS limitations.

- **Requirement for informed consent.** INTERMACS and the NHLBI are preparing the groundwork to eliminate the requirement for informed consent. This effort has been an exhaustive process of legal review including review by the INTERMACS OSMB and discussions with CMS. This will be put through the IRB process within the next 6 months.
- **Completeness of patient capture.** INTERMACS requires that all participating institutions enter all consenting patients receiving an approved device, whether for BTT or DT indication. This does exclude patients in FDA IDE clinical trials, which would only include new devices or approved devices that are implanted for a non-approved indication. Since March 2009, INTERMACS has required that every patient, even if not consented, be entered into the database with outcomes out to 48 hours. Examination of this data as well as counts of device implants provided by industry (which are made available to INTERMACS) indicates that we miss complete data on an average of 10% of implanted patients. If we are successful in removing the need for informed consent, the percentage of implanted patients receiving approved devices that are entered in the database would approach 100%.

- **Not capturing patient identifiers.** INTERMACS collects detailed patient identifiers: first and last name, partial social security number, date of birth, date of implant, date of death, brand of device, device serial number, implanting hospital, and dates of all major outcomes and adverse events. The next revision of the web-based data entry system to be released in 2014 will include the unique CMS HIC number. Although INTERMACS collects this detailed patient identifying information, the data management and distribution process adheres to all HIPAA PHI regulations and information security requirements. Therefore, data that are used by academicians and others for research purposes (i.e., for purposes not required by law) are “de-identified” to prevent identification of a patient.
- **Auditing process.** INTERMACS has an extensive auditing process that is not the equivalent of a clinical trial, though long term auditing of that level would be totally unaffordable for any national registry. The audit process for INTERMACS includes on-going virtual audits and on-site audits to all participating centers over the course of the five year contract period. Sites are notified 60 days prior to an audit visit. Audited data includes key data fields, as determined by INTERMACS. The INTERMACS nurse monitor contacts the site for a pre-visit phone (virtual) audit approximately 2 weeks before the on-site audit. During the call the monitor reviews site specific summaries for duplicated events, unknown sources of bleeding, unknown causes of death, device explant inconsistencies, and any other noted discrepancies. The sites are requested to make corrections prior to the on-site visit. The pre-visit telephone audits assists the sites to prepare for the on-site audit and allows them the opportunity to ‘clean up’ discrepancies prior to the visit. As a result of the pre-visit telephone audit, the on-site audit is more efficient and allows time for re-education when necessary. In addition to scheduled audits, “for cause” audits are conducted for all sites that have a less than 70% compliance rate.

Audit visits monitor data accuracy of web-based data submissions and information contained in source documents as well as participant performance and progress. The INTERMACS audit process follows a Risk-Based Monitoring approach which emphasizes major outcomes. An example of our key focus elements are: follow-up form completion, reason for no Quality of Life and Functional Capacity data entered, ‘Other’ Causes of Death, ‘Alive’ greater than 4 years post implant, and implant and explant inconsistencies. “For Cause” and Intermediate Cause audit visits are made as indicated by the Hospital Standards Committee.

The audit process will continue to identify member institutions that perform poorly in data submission compliance. INTERMACS identifies and works with these underperformers to identify reasons for low rates of data collection and/or tardy data submission. These institutions are retrained on proper data collection methods with the goal of identifying and overcoming obstacles to submission.

- **Compliance with Follow-up Forms.** The institutional performance regarding timely data submission has improved substantially with the ongoing feedback provided to the sites. In 2010, 69% of sites had > 90% compliance with the scheduled follow-up forms after device implantation. By 2012, this had increased to 85% site compliance of all registered sites.

- **Quality of Life and Functional Outcomes Data.** As discussed, we are now extending the same intervention to increase compliance with reporting of Quality of Life and Functional Outcomes, as well as for the survival and transplant outcomes above. During the early years of INTERMACS, quality of life and functional outcomes data were not considered standard of care in most institutions and were rarely collected (and therefore not entered into INTERMACS). INTERMACS has led the way in defining the new priority to obtain this information as part of the standard clinical care of all patients with durable devices.⁶ Also newly required is specification of the reason for non-completion. Since May 2012, the completion of the EuroQoL quality of life instrument has increased as we provide benchmarks to sites. The pre-implant rate of completion has risen from 45% to 54% pre-implant and the 1 year survey completion increased from 55% to 64%. This effort will now be markedly enhanced by the stated focus of CMS on these data elements as a measure of quality at the individual sites. These and other parameters deemed critical to CMS and the FDA can be tailored as the focus of feedback and benchmarking to individual sites.

In conclusion, while we are pleased that CMS has found INTERMACS useful in providing data to establish the survival benefit of contemporary durable circulatory assist devices, proper assurance of hospital performance and informed patient/physician decisions in a rapidly evolving field requires continued long-term data collection on all patients receiving these expensive devices.

Therefore, we propose the following language to the Decision in order to formalize hospital participation in an audited registry that provides long-term patient follow-up as a condition for credentialing, such action by CMS will assure the sustainability of INTERMACS as a vital resource:

“2.b.i.i Facilities must track patient outcomes for the duration of patient follow-up, including survival, adverse events (e.g., bleeding, infection, stroke, and device malfunction), functional status, and quality of life through participation in a national audited registry that collects long term data which allows comparisons with other institutions and facilitates monitoring internal quality improvement.”

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