



**John Marks, Ph.D.**

***Assessment of Neurologic and  
Neurocognitive Function  
What are the Challenges?  
What is Reasonable?***

***Presented by  
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***Pediatric Assessments of Neurological and Neurocognitive  
Function for Cardiovascular Devices FDA Sponsored Workshop***

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# Affiliations and Product Regulatory Status

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**I am the Director of Clinical Research for Levitronix LLC and have a financial interest in the company.**

**Levitronix is a developer of magnetic “Mag Lev” VADs designed for the treatment of heart failure.**

**Levitronix VAD products, with the exception of the CentriMag RVAD, are investigational in the U.S. and are not cleared by the FDA for the treatment of heart failure.**

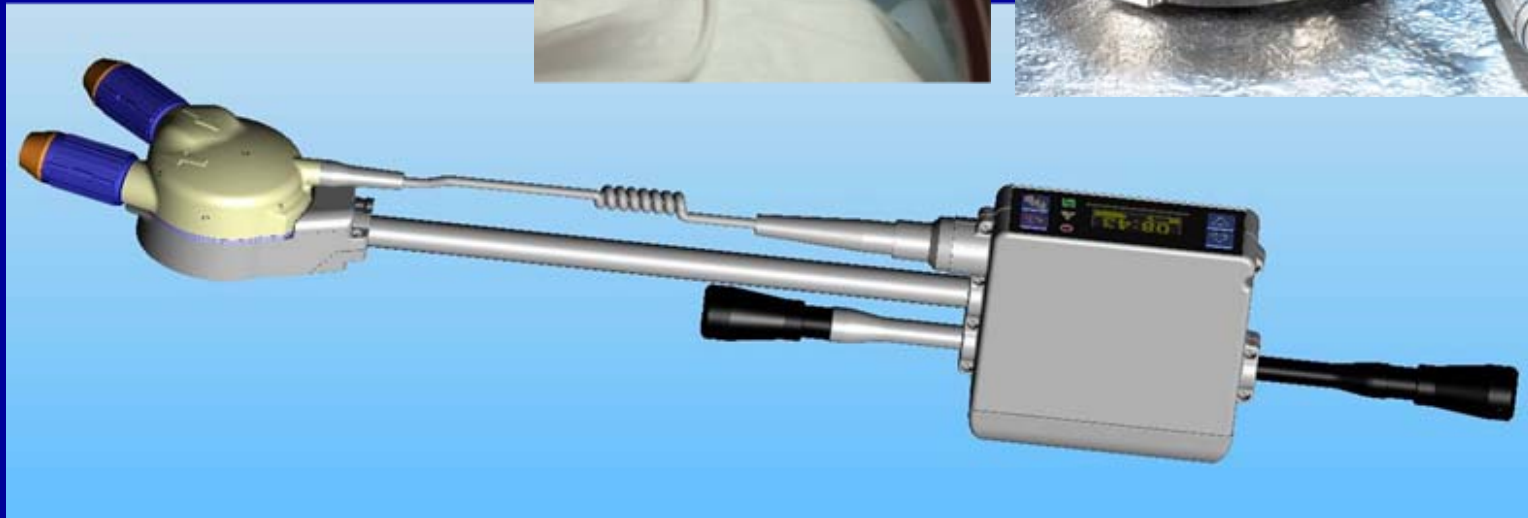
# Levitronix®

All Levitronix Ventricular Assist Systems are designed to serve as a “**bridge-to-decision**” or as “**bridge-to-bridge**” for support of patients who have failed conventional therapy and are in need of mechanical circulatory support to sustain life.



# Levitronix Core Medical Systems

- CentriMag
- PediMag
- UltraMag



# Neurologic Events During Circulatory Support

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“Neurological events are among the most commonly reported complications after placement of LVADs. **Cerebral embolism** is the most frequent brain event, with reports ranging from **3% to 47%** . . . .”

Lazar et al. Neurologic Events During Long-Term Mechanical Circulatory Support for Heart Failure  
Circulation 2004;109:2423

# CNS Complications During VAD Bridge to Heart Transplantation

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- Data from 23 centers
- Patients 1 day to <18 years
- **99 (4%) patients** bridged to transplantation
- 77% survival to transplantation
- **19%** incidence of stroke

Blume et al. Outcomes of Children bridged to Heart Transplantation with Ventricular Assist Devices. Circulation 2006 113:2213

# CNS Complications During ECMO

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“Data concerning **4,942** patients who underwent one run of ECLS were analyzed. **Six hundred thirty-six patients (13%)** developed acute, severe CNS complications.”

Cengiz et al. Central Nervous System Complications During Pediatric Extracorporeal Life Support: Incidence and Risk Factors. Crit Care Med 2005;33(12):2817

# Case Study: Neurologic Assessment

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- **CentriMag VAD**
- **U.S. Clinical Trials**
- **Started in Jan 2004**
- **“Bridge to Decision”**



**FDA Guidelines (2003 DRAFT):  
Recommendations, Suggestions & Possible Tests**

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**Assessments of Neurological/  
Neurocognitive Function**

**Guidance Document**

**2003 DRAFT**

# FDA Guidelines (2003 DRAFT): Recommendations, Suggestions & Possible Tests

## 2. Testing Domains

The following are the recommended neurological domains to be evaluated during the clinical investigation. Examples of possible tests are included under each domain. These examples are not meant to be prescriptive or all-inclusive; rather, they are suggested possibilities to consider when designing a battery of tests:

- **Clinical Stroke**
  - NIH Stroke Score or its amended versions
- **Mood and Affect**
  - Beck Depression Score
  - Center for Epidemiology Scale for Depression (CDC)
  - Hamilton Depression Inventory

- 28 Tests
- 10 Domains
- For MCS < 30 Days  
the only test required  
is the NIHSS required

- **Cognitive Function (all 7 areas listed below should be addressed)**
  - **Concentration/Attention**
    - Digit Span (Wechsler Adult Intelligence Scale – Third Edition)
    - Mental Control (Wechsler Memory Scale – Revised)
  - **Memory**
    - Wechsler Memory Scale – Revised (Paragraph Memory, Visual Reproduction)
    - Rey Auditory Verbal Learning Test
    - California Verbal Learning Test
    - Hopkins Verbal Learning Test
  - **Language**
    - Subtests of Boston Diagnostic Aphasia Examination
    - Boston Naming Test
    - Controlled Oral Word Association Test (FAS)
  - **Visual/Spatial Perception**
    - Rey Complex Figure Test (Copy)
    - Block Design (Wechsler Adult Intelligence Scale – Third Edition)
  - **Processing Speed**
    - Digit Symbol (Wechsler Adult Intelligence Scale – Third Edition)
    - Symbol Search (Wechsler Adult Intelligence Scale – Third Edition)
    - Symbol Digit Modalities Test
  - **Motor Function**
    - Grooved Pegboard
    - Finger Oscillation
    - Purdue Pegboard
    - Grip Strength
  - **Abstract/Executive Function**
    - Stroop Test
    - Booklet Category Test
    - Wisconsin Card Sorting Test
- **Collaborative Testing (evaluation by family members)**
  - Stroke Impact Scale
  - Stroke Specific Quality of Life Scale
  - Neuropsychological Inventory Scale

# Case Study: Neurologic Assessment during VAD Trial

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- **Serial Assessments**
  - **NIH Stroke Scale**
  - **Glasgow Coma Scale**
- **Neurologic Adverse Events**
  - **INTERMACS Definition**



# Case Study: Neurologic Assessment during VAD Trial

- Clinic Trials ongoing
- Patients enrolled: 49
- Patients discharged: 22
- **GCS - Baseline : 30 patients**
- **NIHSS - Baseline : 1 patient**
- **NIHSS w/ VAD Support : 0 pts.**
- Neurologic AEs: 4 patients
- RVAD cleared for 30 day HDE use



# Lessons Learned - Challenges for Today

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- Most of the patients studied were “emergent”, enrolled while in an O.R. and supported for short durations (< 30 days).
- Neurologic testing prior to and during VAD support was often difficult and when conducted the results were often suspect.
- Many neurologic tests considered were not appropriate for use with the populations being studied or the environments in which the patients were being treated.
- Difficult to assess whether the neurologic injuries were pre-existing, or device related.
- From a regulatory perspective reporting of the incidence, recovery or persistence of neurologic dysfunction may be sufficient, or preferable to the use of standardized instruments.

# Objectives of VAD Support

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- **Acute Support**
  - Bridge – to – Bridge
  - Bridge – to – Decision
  - Bridge – to – Recovery
- **Chronic Support**
  - Destination Therapy
  - Bridge – to - Transplantation

# Challenges (or What did we learn from this experience?)

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- **Most of the patients studied were “emergent”, enrolled while in an O.R. and supported for short durations (< 30 days).**
- **Neurologic evaluation prior to and during support was often difficult or impossible with the tools selected.**
- **Many of the recommended or suggested neurologic and neuro-cognitive tests were not be appropriate for use with the populations being studied and in the environments in which the patients were being treated.**
- **When neurologic injury was identified it was difficult to assess whether the injury was device related, pre-existing, or attributable to the underlying disease or some other cause.**
- **From a regulatory perspective reporting of the incidence and recovery or persistence of neurologic dysfunction may be sufficient.**

# ECMO Support for Cardiac Diagnoses

Diagnoses / Age	0 - 30 Days	31 Days - 1 Yr.	1 - 16 Yrs.
<b>Congenital</b>	<b>87.2%</b>	<b>75.9%</b>	<b>41.7%</b>
Cardiac Arrest	1.5%	2.4%	4.2%
Cardiogenic Shock	1.2%	1.6%	3.2%
Cardiomyopathy	1.8%	5.5%	<b>18.9%</b>
Myocarditis	0.9%	2.4%	7.0%
Other	7.4%	12.2%	25.0%

- Analysis of Data from ELSO Registry

# Challenges (or What did we learn from this experience?)

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# FDA DRAFT Guidance Document

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- “Not all patients can undergo pre-device testing”.
- **Alternative baseline:**
  - Use  $\geq 30$  day tests as baseline, or
  - Baseline established when stable
- Follow-up at 6 mo., 12 mo., and later

# FDA DRAFT Guidance Document

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- **“Stable” was defined as:**
  - **SaO<sub>2</sub> > 90%**
  - **Extubated**
  - **No IV or IA lines**
  - **Able to sit up in bed**
  - **Not in an ICU setting**

# Challenges (or What did we learn from this experience?)

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# FDA DRAFT Guidance Document

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- **The tests should be: validated, nationally recognized, with standardized norms for the environment, age and condition of the populations being studied.**
- **Predictive of chronic deficits.**

# ***Predictive Value of Neurological Assessments***

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***“An abnormal result in a single age-specific neonatal neurological examination ..... **did not reliably predict** the future development of an individual child.”***

*Lano AI. The value of neonatal neurological assessment in predicting neurodevelopmental problems at preschool. Dissertation. Dept. of Child Neurology, U. Helsinki. 2002*

# Challenges (or What did we learn from this experience?)

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# Perioperative Stroke in Infants

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- Half (50%) of the neonates and infants undergoing operations for congenital heart disease had evidence of **preoperative stroke** .
- Incidence of perioperative stroke was **10%**.
- Most were clinically silent and undetectable without neuroimaging.

Chen J et al, Perioperative stroke in infants undergoing open heart operations for congenital heart disease. Ann Thorac Surg. 2009 Sep;88(3):823.

# Challenges (or What did we learn from this experience?)

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- Many of the recommended or suggested neurologic and neuro-cognitive tests were not be appropriate for use with the populations being studied and in the environments in which the patients were being treated.
- When neurologic injury was identified it was difficult to assess whether the injury was device related, pre-existing, or attributable to the underlying disease or some other cause.
- **From a regulatory perspective reporting of the incidence, recovery or persistence of neurologic dysfunction may be sufficient, or preferable to the use of standardized instruments.**

# INTERMACS Definition: Neurologic Dysfunction

Any new, temporary or permanent, focal or global **neurological deficit** ascertained by a **standard neurological examination** (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note).

The examining physician will distinguish between a **transient ischemic attack (TIA)**, which is fully reversible within 24 hours (and without evidence of infarction), and a stroke (**CVA**), which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction).

The NIH Stroke Scale (for patients > 5 years old) must be re-administered at 30 and 60 days following the event to document the presence and severity of neurological deficits. Each neurological event must be subcategorized as:

- 1) Transient Ischemic Attack (acute event that resolves completely within 24 hours with no evidence of infarction).
- 2) Ischemic or Hemorrhagic Cardiovascular Accident/CVA (event that persists >24 hours or < 24 hours associated with infarction on an imaging study).

In addition, to above, for patients < **6 months of age**, any of the following:

- 3) New abnormality of head ultrasound
- 4) EEG positive for seizure activity with or without clinical seizure

# Conclusions: Factors to Consider

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- Most of the patients studied will be “emergently” supported
- Support will be for short duration (<30 days).
- Methodology for assessment of neurologic function may need to be specific for different populations and indications for use.
- Establishing neurologic baseline prior to support will be difficult. Alternatives to consider include the use of historic or “when stable” baselines.

# Conclusions: Recommendations

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- **Finalize the DRAFT FDA Guidance document**
- **Provide guidance for how to assess if an injury pre-existed, was device related, or attributable to the underlying disease.**
- **Establish a standard definition (eg. INTERMACS) for reporting the existence and severity of neurologic injuries.**

# Conclusions:

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- **Given the complexity of the pediatric populations and the environments in which treatment will occur:**
  - **Are the standardized tests (instruments) we plan to discuss today able to be administered in a controlled and reproducible manner?**
  - **Are these tests sufficiently validated or understood to serve as “gatekeepers” for the introduction of new technologies?**
- **Consider whether documenting the incidence, recovery, and persistence of neurologic dysfunction may be sufficient to approve a device, versus relying on standardized instruments.**

# Conclusions:

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- **Are standardized neurological assessments, such as imagining and routine neurological evaluations of response to stimulus, motor function, etc. sufficient for regulatory approval today?**
- **Are we ready for a paradigm shift from the use of the established clinical assessment and reporting of neurologic dysfunction, or it too soon and uncertain to base regulatory approvals on alternative instruments?**

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***Thank you for opportunity to present  
to this distinguished group.***

