

# Pediatric INTERMACS Update

## *Interagency Registry for Mechanically Assisted Circulatory Support*

---

Christopher Almond MD MPH  
Children's Hospital Boston

*Fourth International Conference on Pediatric Circulatory Support  
Systems and Pediatric Cardiopulmonary Perfusion*

*Portland, Oregon  
May 23, 2008*

# Disclosure Statement

---

*Pediatric INTERMACS Report  
Christopher Almond MD, MPH*

- I will discuss off label and/or investigational use of pediatric ventricular assist devices
- The following relevant relationships exist related to my role in this session:
  - *Berlin Heart, Inc, (Consultant and Co-PI of the Berlin Heart IDE Clinical Trial)*

# Objectives

---

- To briefly review the purpose, background and organizational structure of INTERMACS
- To review data from the first 18 months of INTERMACS since official launch in June 2006
- To review the pediatric data available to date
- To discuss some of the challenges and opportunities specific to pediatric INTERMACS moving forward

# Objectives

---

- To briefly review the purpose, background and organizational structure of INTERMACS
- To review data from the first 18 months of INTERMACS since official launch in June 2006
- To review the pediatric data available to date
- To discuss some of the challenges and opportunities specific to pediatric INTERMACS moving forward

# What is INTERMACS?

---

- Interagency Registry for Mechanically Assisted Circulatory Support
- Federally supported national VAD registry of *approved* durable mechanical circulatory support devices
- Joint effort between:
  - NHLBI
  - CMS
  - FDA } *Interagency*
  - Clinicians and scientists
  - Industry

# Why is a registry of approved devices actually necessary?

---

Despite rigorous pre-market testing, important public safety concerns may emerge about a medical therapy only after it is used outside the confines of a clinical trial

Vioxx

Thalidomide

Coronary stents

Defibrillators

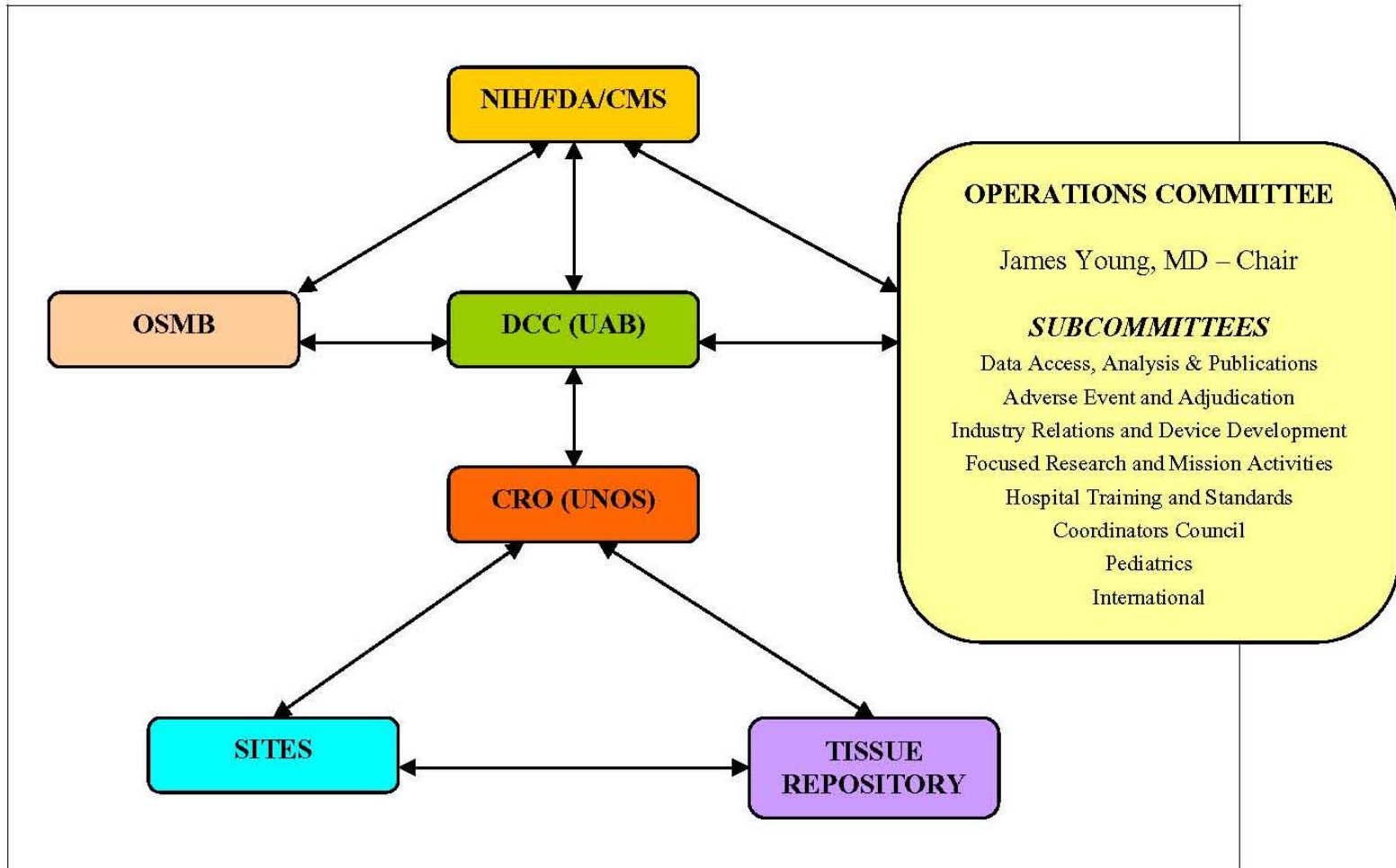
# What are the goals of INTERMACS?

---

- To better characterize device performance as used in the broader population
- To optimize patient outcomes and refine patient selection for VAD therapies
- To develop 'best practices' through careful analysis of complications and adverse events
- To guide the development of the next generation of devices
- To promote basic and translational research in the substrate of advanced heart failure

# What is the organization structure?

## General Organizational Chart



NIH - National Institutes of Health  
 CMS - Center for Medicare and Medicaid Services  
 DCC - Data and Clinical Coordinating Center  
 UNOS - United Organ Sharing Services

FDA - Food and Drug Administration  
 OSMB - Observational Safety Monitoring Board  
 UAB - University of Alabama at Birmingham

# Objectives

---

- To briefly review the purpose, background and organizational structure of INTERMACS
- To review data from the first 18 months of INTERMACS since official launch in June 2006
- To review the pediatric data available to date
- To discuss some of the challenges and opportunities specific to pediatric INTERMACS moving forward

# Overview of INTERMACS Data

**Implant Dates:** June 23, 2006 – December 31, 2007

**Follow-up Date:** December 31, 2007

---

**Total Hospitals Enrolled:** 89

**Hospitals that have contributed data:** 75

---

**Total Patients:** 511

**Retrospective:** 91

**Prospective:** **420**

---

**Note:** Analyses examine these 420 prospective patients

# Participation by state (N=89 centers)



<b>Gender:</b>	<b>Males</b>	<b>328 (78%)</b>
	<b>Females</b>	<b>92 (22%)</b>

---

<b>Race:</b>	<b>White</b>	<b>302 (72%)</b>
	<b>African American</b>	<b>86 (20%)</b>
	<b>Other</b>	<b>32 ( 8%)</b>

---

## **Age at Implant:**

<b>mean:</b>	<b>50.9 yrs</b>
<b>range:</b>	<b>4.5 to 79.0</b>
<b>≤18 yrs:</b>	<b>11 (3%)</b>

## Implants:

<u>Support</u>	<u>N (%)</u>
LVAD:	314 (75%)
RVAD:	5 (1%)
Bi-VAD:	77 (18%)
TAH:	24 (6%)
<hr/>	
Total:	420 (100%)

# Strategy of Support (N=420)

<b><u>Device Strategy at Implant</u></b>	<b><u>n</u></b>	<b><u>% of 420</u></b>
Bridge to Recovery	21	5%
Bridge to Transplant*	336	80%
Listed	179	43%
Likely to be listed	83	20%
Moderate likely to be listed	44	10%
Unlikely to be listed	30	7%
Destination Therapy	63	15%
<b>Total</b>	<b>420</b>	<b>100%</b>

\*In all subsequent slides “Bridge to Transplant” will include the four subcategories.

## Overall:

Deaths (prior to transplant): 104 (24%)

Transplants: 156 (37%)

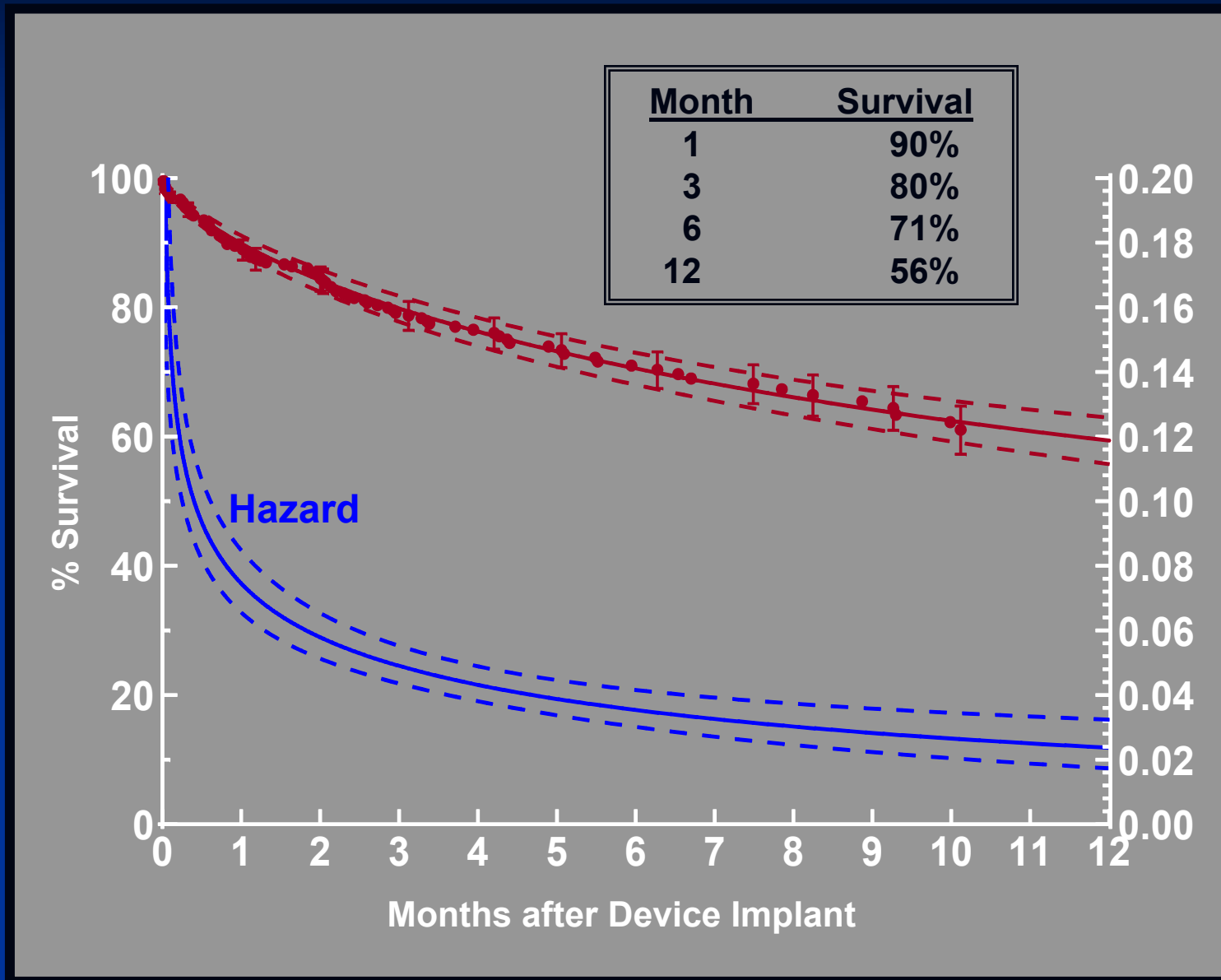
Recovery: 11 ( 3%)

Alive (device in place): 149 (36%)

---

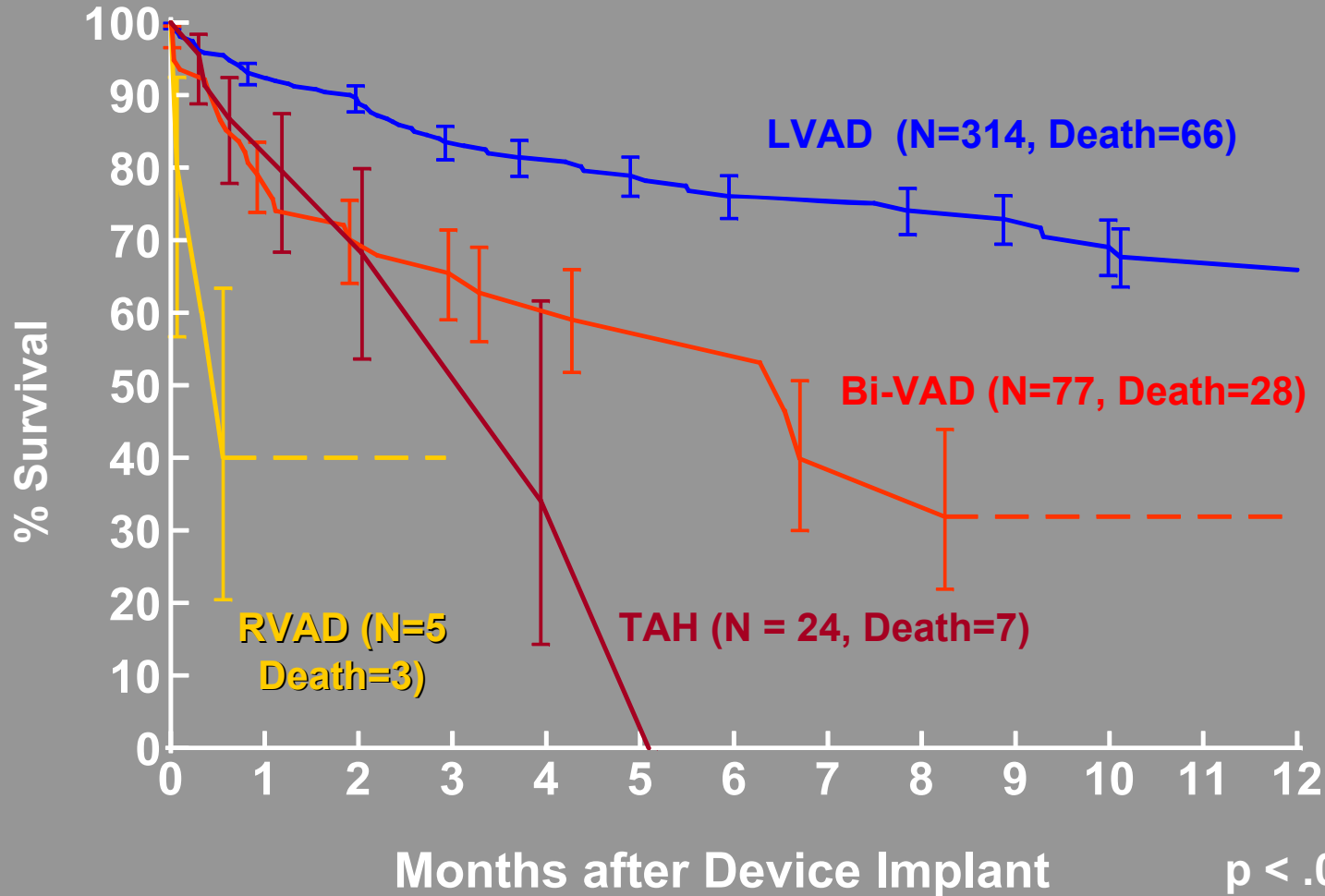
Total 420 (100%)

# Overall Outcomes (N=420)

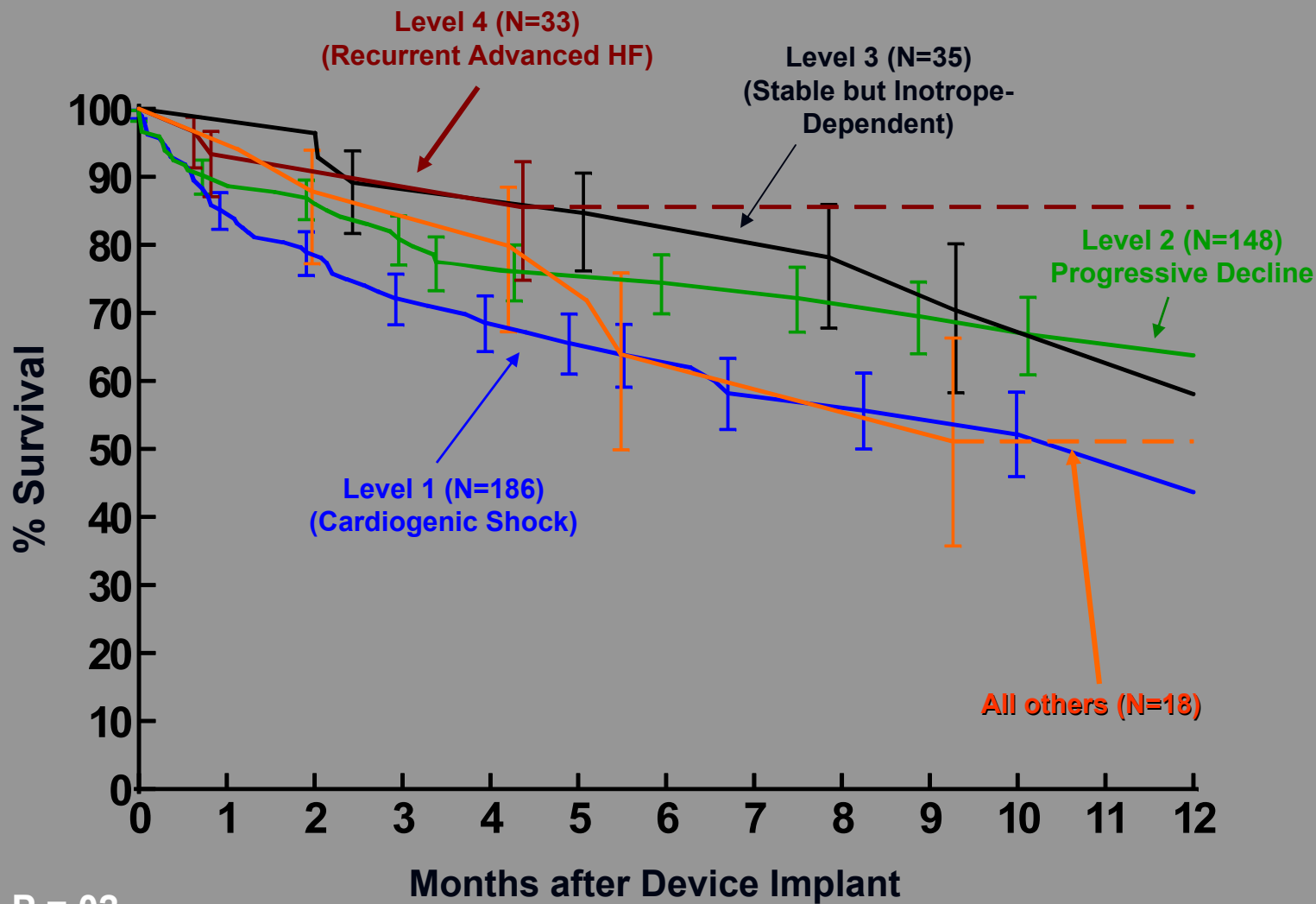


Deaths / Month

# Type of Device (n=420)



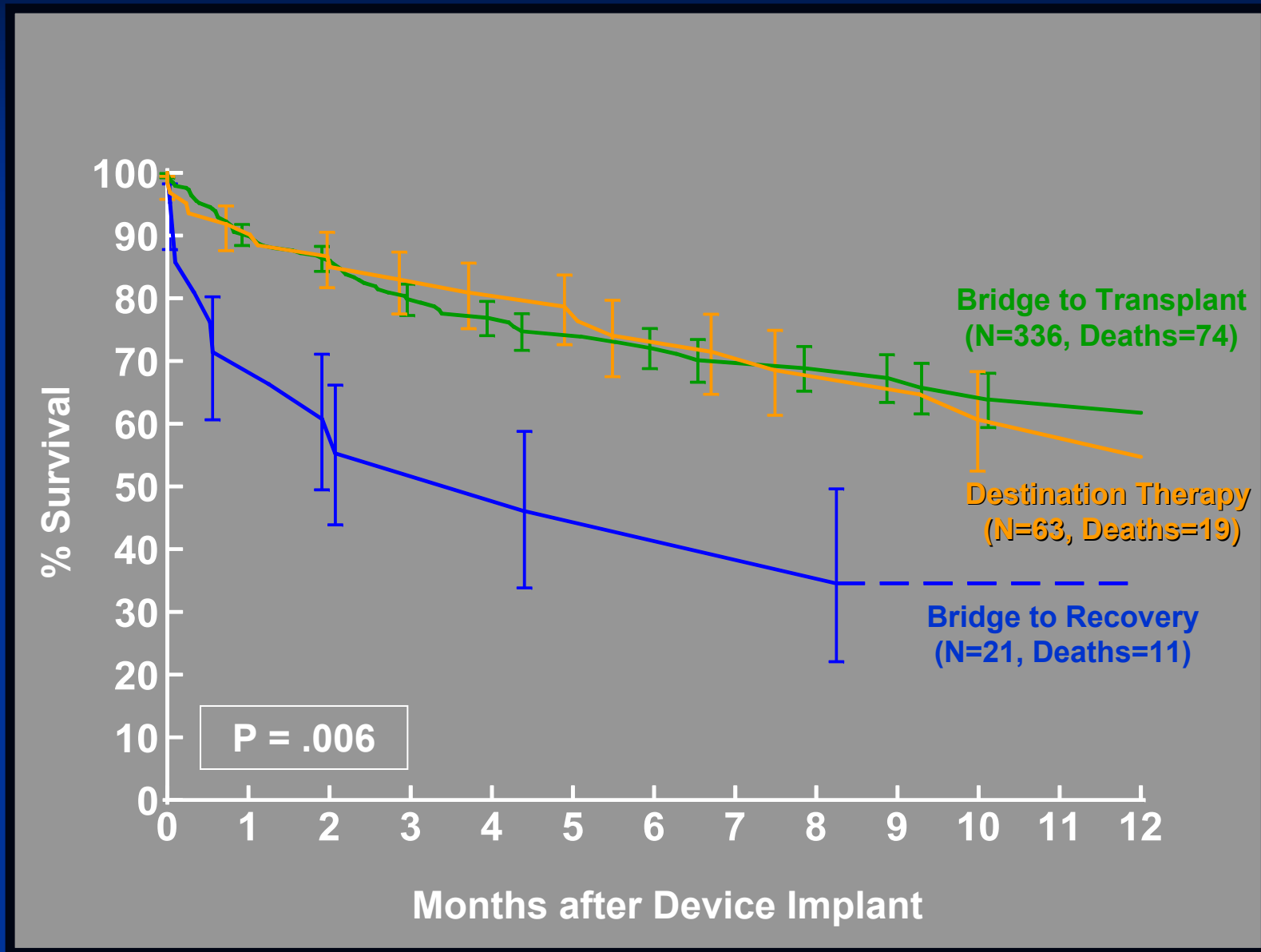
# Patient Profile at implant (N=420)



P = .02

Event: Death (censored at transplant)

# Device Strategy at Implant (N=420)

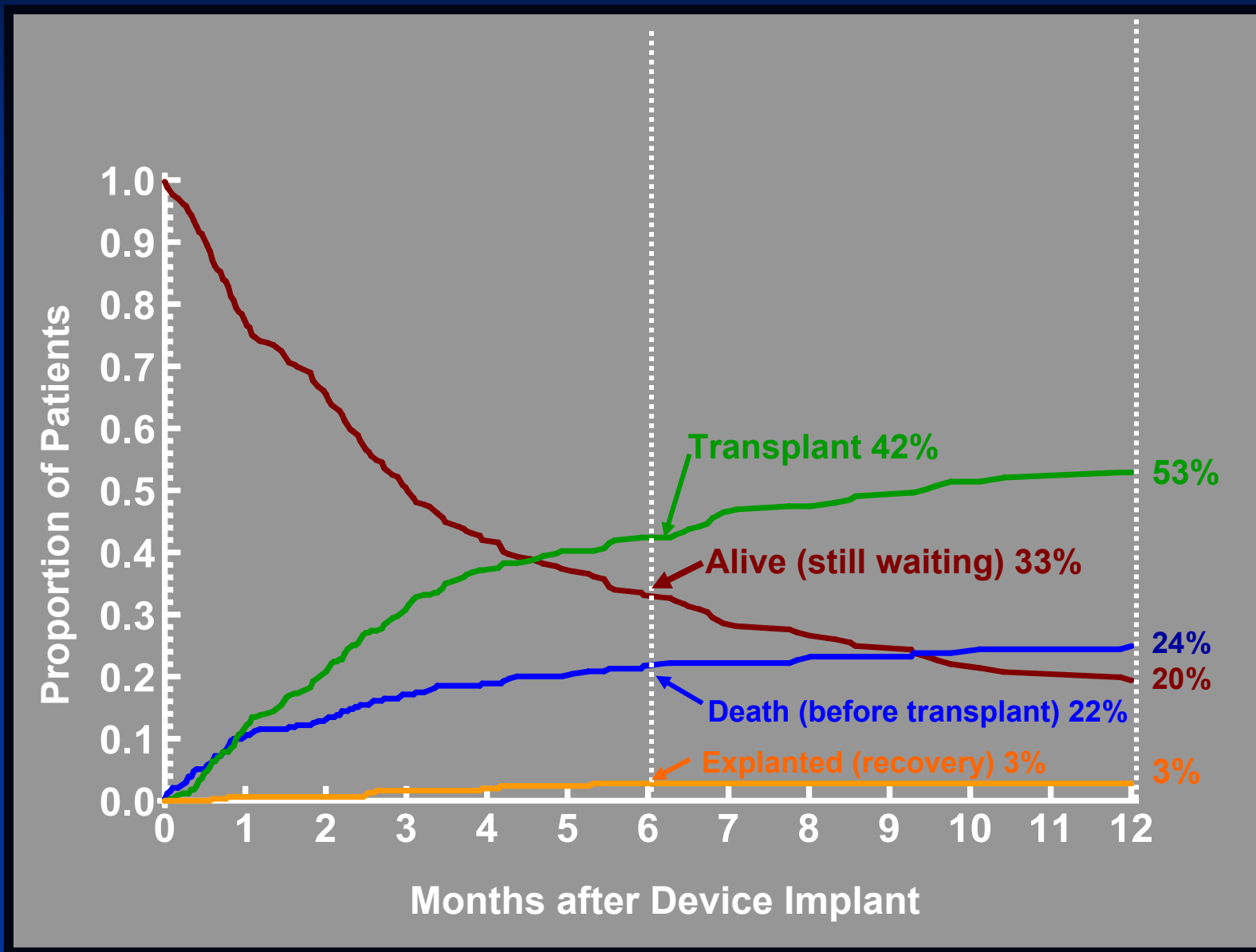


# Primary Cause of Death (N=420)

Primary Cause of Death	Early ( $\leq 1$ mo)		Later ( $> 1$ mo)		Total	
	n	% of 42	n	% of 62	n	% of 104
CNS Event	6	14.3%	13	21.0%	19	18.3%
Multi-Organ Failure	8	19.0%	9	14.5%	17	16.4%
Cardiac Failure*	10	23.8%	6	9.7%	16	15.4%
Infection	1	2.4%	7	11.3%	8	7.7%
Respiratory Failure	3	7.1%	5	8.1%	8	7.7%
Device Failure	1	2.4%	4	6.5%	5	4.8%
Hepatic Failure	4	9.5%	0	0%	4	3.8%
Pulmonary Embolism	2	4.8%	1	1.6%	3	2.9%
Surgical Bleeding	1	2.4%	2	3.2%	3	2.9%
GI Bleed	0	0%	2	3.2%	2	1.9%
Renal Failure	1	2.4%	1	1.6%	2	1.9%
Other	5	11.9%	12	19.4%	17	16.4%
<b>Total</b>	<b>42</b>	<b>100.0%</b>	<b>62</b>	<b>100.0%</b>	<b>104</b>	<b>100.0%</b>

\*Cardiac Failure includes RV Failure and VT/VF

# Bridge to Transplant (N=336)



<b>Risk Factors for Death</b>	<b>Relative Risk</b>	<b>p-value</b>
<b>InterMACS Level 1</b>	<b>1.59</b>	<b>.02</b>
<b>Age (older)*</b>	<b>1.41</b>	<b>&lt; .001</b>
<b>Ascites</b>	<b>2.04</b>	<b>.003</b>
<b>Bilirubin (higher)**</b>	<b>1.49</b>	<b>.05</b>
<b>Bi-VAD Implant</b>	<b>2.12</b>	<b>.002</b>
<b>Total Artificial Heart</b>	<b>2.41</b>	<b>.03</b>

\*Compares increased risk from age 50 to 60 years

\*\*Compares increased risk from bilirubin = 1 to 6(mg/dl)

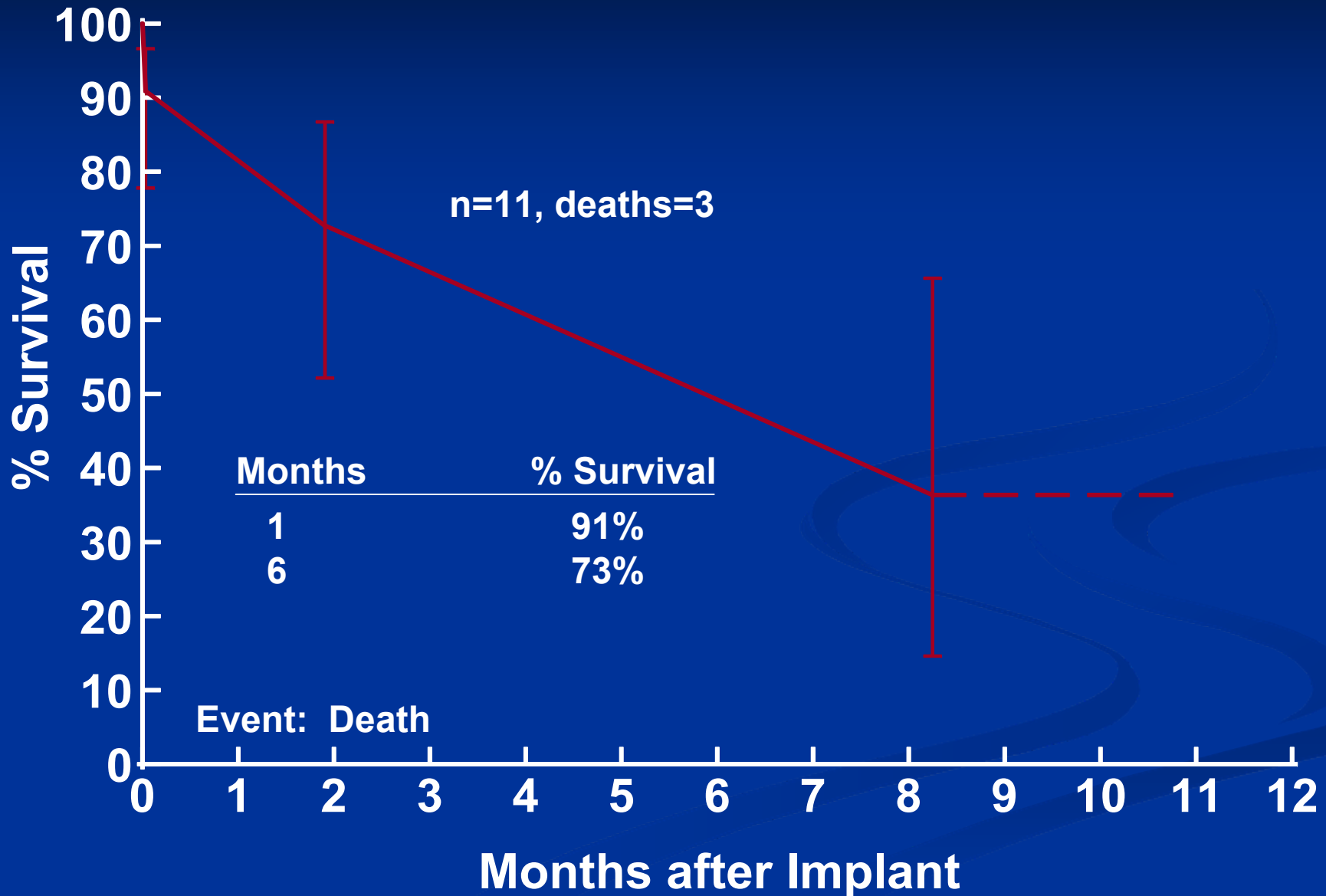
# Objectives

---

- To briefly review the purpose, background and organizational structure of INTERMACS
- To review data from the first 18 months of INTERMACS since official launch in June 2006
- To review the pediatric data available to date
- To discuss some of the challenges and opportunities specific to pediatric INTERMACS moving forward

# Pediatric Experience (N=11)

N=11, prospective pediatric patients (age at implant < 19 years)



# Objectives

---

- To briefly review the purpose, background and organizational structure of INTERMACS
- To review data from the first 18 months of INTERMACS since official launch in June 2006
- To review the pediatric data available to date
- To discuss some of the challenges and opportunities specific to pediatric INTERMACS moving forward

# Perhaps our greatest challenge...

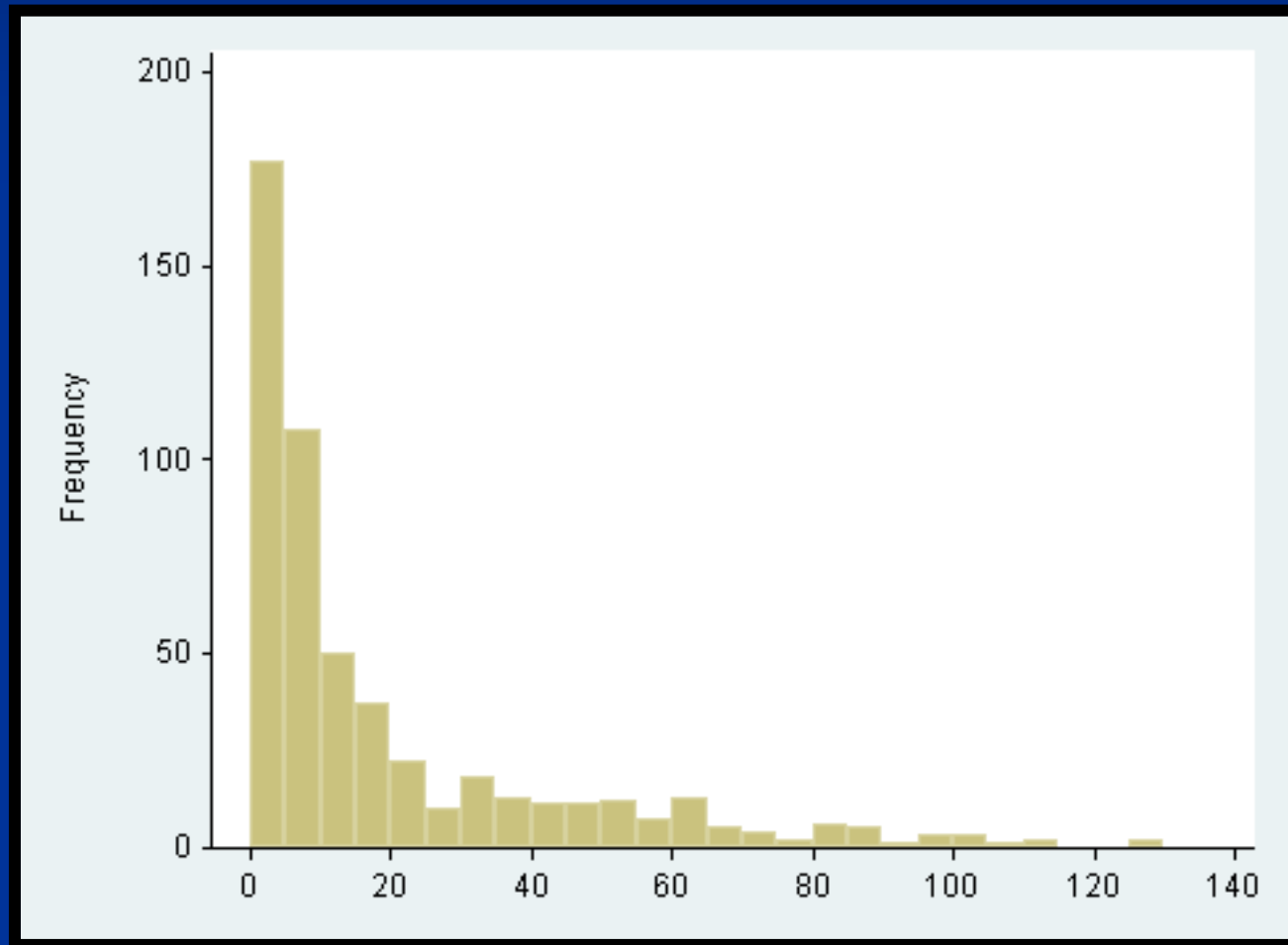
---

- The number of children with severe heart failure who died on the heart transplant waitlist between 1999-2006....

**533**

- The highest waitlist mortality rate in solid-organ transplantation medicine
- One in six children overall; one in five on inotropic support, one in four with CHD, one in 3 on ECMO
- Mortality rate more than two-fold higher than adults

# Weight distribution of children who died on the waitlist between 1999 and 2006 (N=533)



# FDA-approved VADs

---

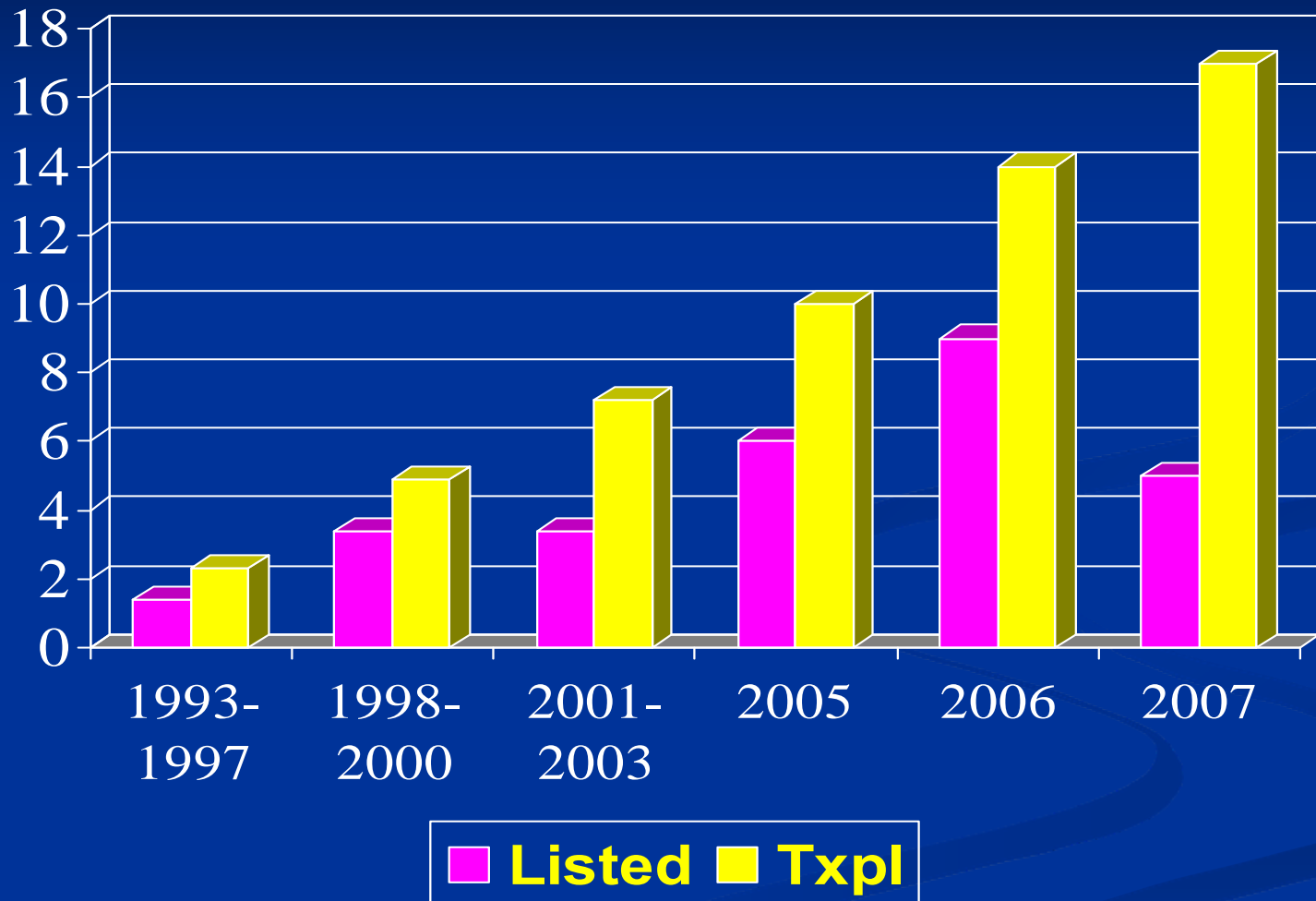
## Adult

HeartMate IP  
HeartMate XV  
HeartMate XVE  
HeartMate II  
Thoratec IVAD  
Thoratec PVAD  
Abiocr TAH (HDE)  
Novacor PC  
Novacor PCq  
Syncardia CardioWest

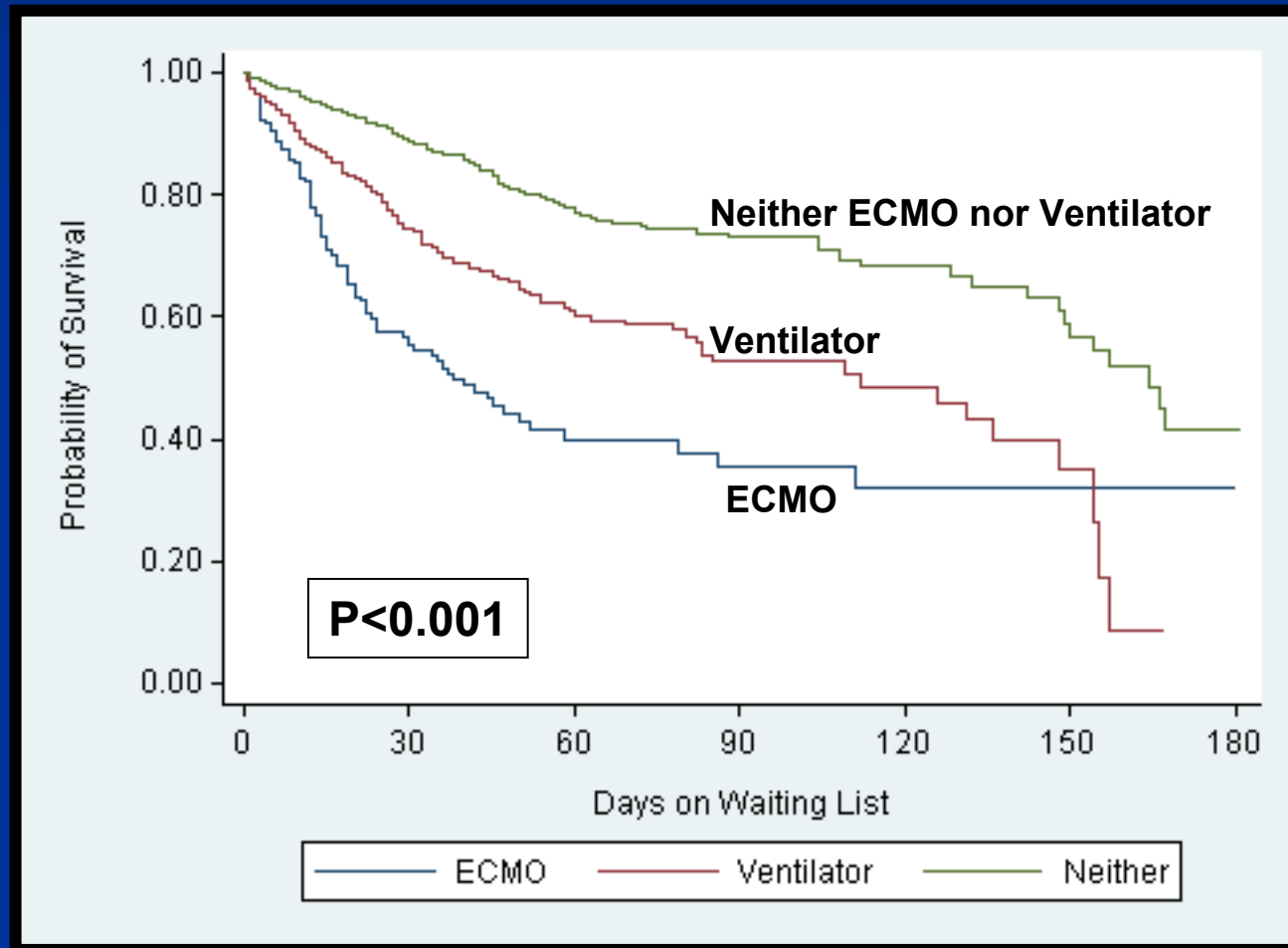
## Pediatric

Debakey-VAD Child

# Pediatric VAD use



# Which children listed status 1A are at highest risk for death on the wait list and may benefit from support?



# Risk-stratification of Status 1A Patients

	7-day	14-day	30-day	60-day	90-day	6-month	Overall
<b>All status 1A candidates (N=1874)</b>	4.9%	8.5%	13.7%	18.0%	18.9%	20.3%	21.1%
<b>ECMO (N=346)</b>	10.1%	17.9%	25.7%	29.8%	30.4%	30.6%	31.5%
<b>Cardiomyopathy</b>	<b>5.7%</b>	<b>11.4%</b>	<b>15.7%</b>	<b>21.4%</b>	<b>21.4%</b>	<b>21.4%</b>	<b>24.3%</b>
≥10kg (N=34)	0%	8.8%	14.7%	23.5%	23.5%	23.5%	26.5%
<10kg (N=36)	11.1%	13.9%	16.7%	19.4%	19.4%	19.4%	22.2%
<b>Myocarditis</b>	<b>7.7%</b>	<b>12.8%</b>	<b>20.5%</b>	<b>23.1%</b>	<b>23.1%</b>	<b>25.6%</b>	<b>25.6%</b>
≥10kg (N=26)	3.9%	7.7%	15.4%	15.4%	15.4%	19.2%	19.2%
<10kg (N=13)	15.4%	23.1%	30.8%	38.5%	38.5%	38.5%	38.5%
<b>Congenital Heart Disease</b>	<b>11.4%</b>	<b>19.0%</b>	<b>28.0%</b>	<b>32.2%</b>	<b>33.2%</b>	<b>33.2%</b>	<b>33.2%</b>
≥10kg (N=50)	5.4%	14.0%	17.0%	21.4%	25.0%	25.0%	25.0%
<10kg (N=155)	13.6%	20.7%	31.6%	36.1%	36.1%	36.1%	36.1%
<b>Mechanical ventilation (N=570)</b>	6.0%	10.4%	17.0%	22.1%	23.5%	25.1%	25.4%
<b>Cardiomyopathy</b>	<b>4.7%</b>	<b>8.4%</b>	<b>15.7%</b>	<b>16.8%</b>	<b>17.8%</b>	<b>19.4%</b>	<b>19.4%</b>
≥10kg (N=69)	10.1%	17.4%	27.5%	29.0%	29.0%	29.0%	29.0%
<10kg (N=122)	1.6%	3.3%	9.0%	9.8%	11.5%	13.9%	13.9%
<b>Myocarditis</b>	<b>2.3%</b>	<b>6.8%</b>	<b>6.8%</b>	<b>9.1%</b>	<b>9.1%</b>	<b>9.1%</b>	<b>11.3%</b>
≥10kg (N=20)	5.0%	15.0%	15.0%	15.0%	15.0%	15.0%	20.0%
<10kg (N=22)	0%	0%	0%	4.6%	4.6%	4.6%	4.6%
<b>Congenital Heart Disease</b>	<b>7.3%</b>	<b>12.6%</b>	<b>19.6%</b>	<b>27.3%</b>	<b>29.0%</b>	<b>30.8%</b>	<b>31.1%</b>
≥10kg (N=55)	9.1%	14.6%	16.4%	25.5%	27.3%	27.3%	27.3%
<10kg (N=231)	6.9%	12.1%	20.4%	27.7%	29.4%	31.6%	32.0%
<b>No ventilation or ECMO (N=958)</b>	2.3%	4.1%	7.4%	11.3%	12.1%	13.8%	14.7%
<b>Cardiomyopathy</b>	<b>1.3%</b>	<b>2.3%</b>	<b>4.4%</b>	<b>6.4%</b>	<b>6.0%</b>	<b>7.2%</b>	<b>7.7%</b>
≥10kg (N=263)	0.8%	1.5%	3.8%	4.9%	5.7%	5.7%	6.1%
<10kg (N=127)	2.4%	3.9%	5.5%	9.5%	9.5%	10.2%	11.0%
<b>Myocarditis</b>	<b>1.8%</b>	<b>3.6%</b>	<b>7.3%</b>	<b>10.9%</b>	<b>10.9%</b>	<b>12.7%</b>	<b>14.5%</b>
≥10kg (N=45)	2.2%	4.4%	6.7%	11.1%	11.1%	13.3%	15.6%
<10kg (N=10)	0%	0%	10%	10%	10%	10%	10%
<b>Congenital Heart Disease</b>	<b>3.3%</b>	<b>5.6%</b>	<b>10.8%</b>	<b>16.6%</b>	<b>18.0%</b>	<b>21.1%</b>	<b>22.2%</b>
<10kg, no PGE (N=159)	1.9%	4.4%	8.2%	12.6%	14.5%	16.4%	17.0%
≥10kg (N=161)	4.4%	6.8%	13.0%	18.6%	19.9%	24.2%	24.8%
<10kg, PGE (N=107)	3.7%	5.6%	11.2%	19.6%	20.6%	23.4%	26.2%

# INTERMACS and pre-Market Approval

---

- What are the advantages of using INTERMACS as a platform for pre-market studies?
- What might be some potential disadvantages?
- What are some ways that INTERMACS can/is helping to facilitate pre-market approval of emerging devices?

# Advantages of using INTERMACS for pre-market studies?

---

- Central location/website for both pre and post-market data
- Guarantees functionally uniform adverse event definitions, patient profiles, endpoints, follow-up points, etc
- FDA familiarity with the content, process/vehicle
- Benefit from a practice effect (learning curve is steep, studies are among the most complex, less re-inventing the wheel)
- Potential for cost-savings
- Comparisons with predicate devices (control population)


# Challenges to involving INTERMACS in pre-market studies?

---

- Defining “involvement” with INTERMACS – in theory many potential levels of involvement ranging from informal advice to running a pre-market IDE trial
  - Independence of CRO, CEC, DMSB
  - Too many cooks?
- Programming/data field flexibility
- Defining data ownership
- Protecting company secrets to preserve a competitive advantage in a market economy

# 4 Levels of INTERMACS involvement (in pre-market studies)

---

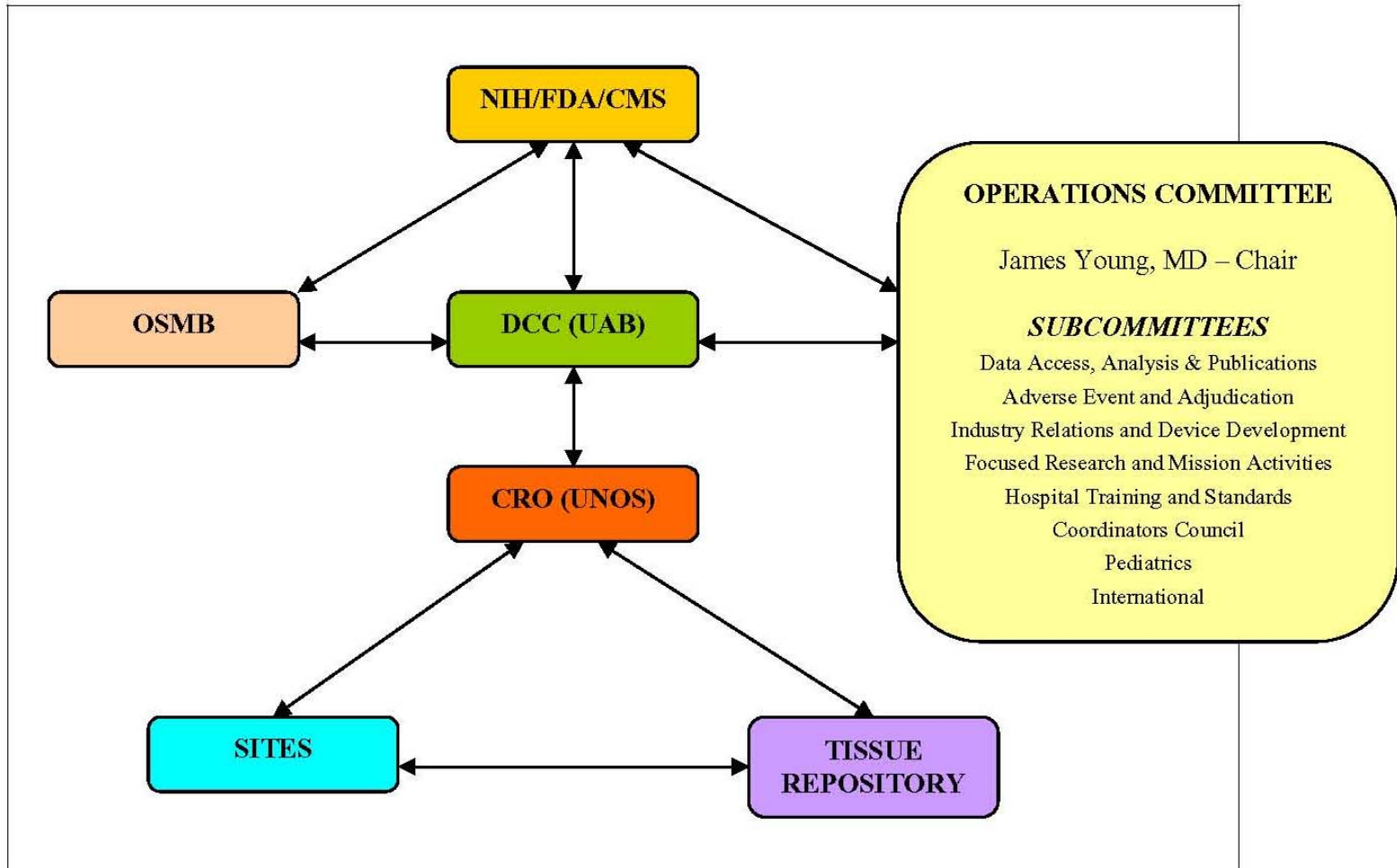
- 
1. Separate altogether including trial definitions, categories and language (e.g. HeartMate II trial)
  2. Separate entities but replicate INTERMACS definitions (e.g. AE's), endpoints, etc (publicly available information and INTERMACS willing to share)
  3. Separate entities but replicate INTERMACS definitions and each contracts with a common private data management company (to facilitate data field exchange, programming, etc)
  4. Completely integrated – sponsor contracts directly with INTERMACS to run pre-market trial (one-stop-shopping model with CRO, DSMB, etc fully integrated)

(1) ...so

**How are Berlin Heart and INTERMACS  
working together?**

**What exactly is the relationship between  
Berlin Heart and INTERMACS?**

## General Organizational Chart

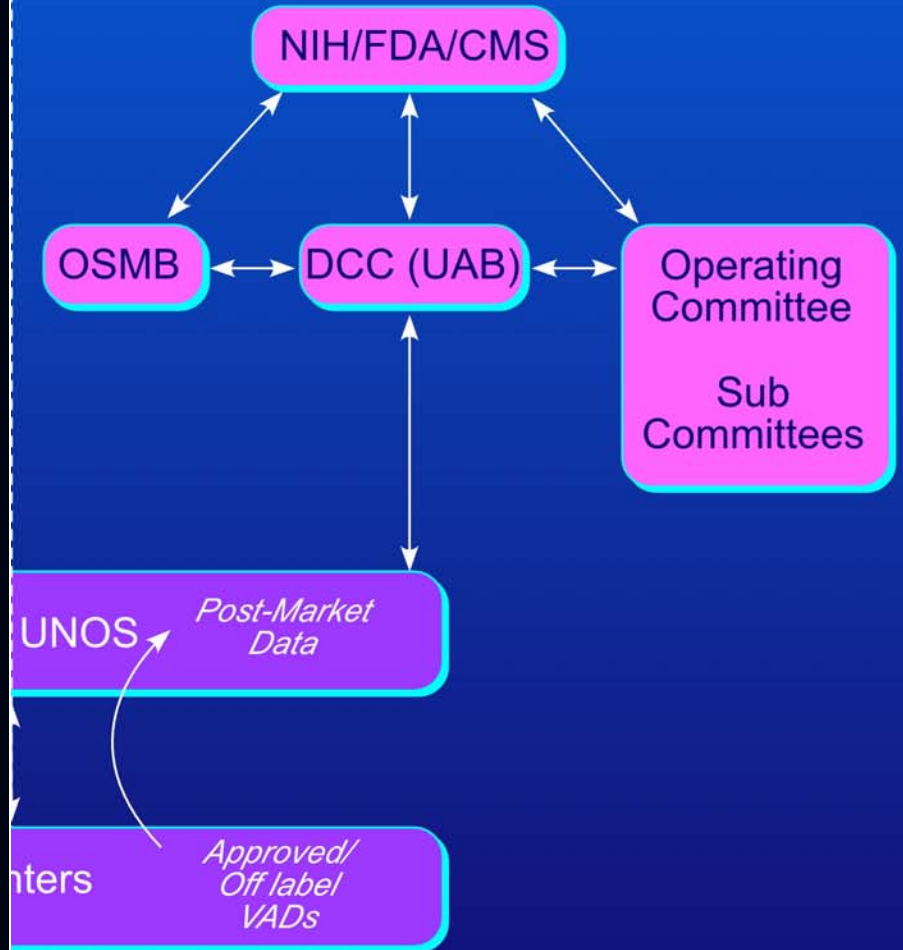


NIH - National Institutes of Health  
 CMS - Center for Medicare and Medicaid Services  
 DCC – Data and Clinical Coordinating Center  
 UNOS – United Organ Sharing Services

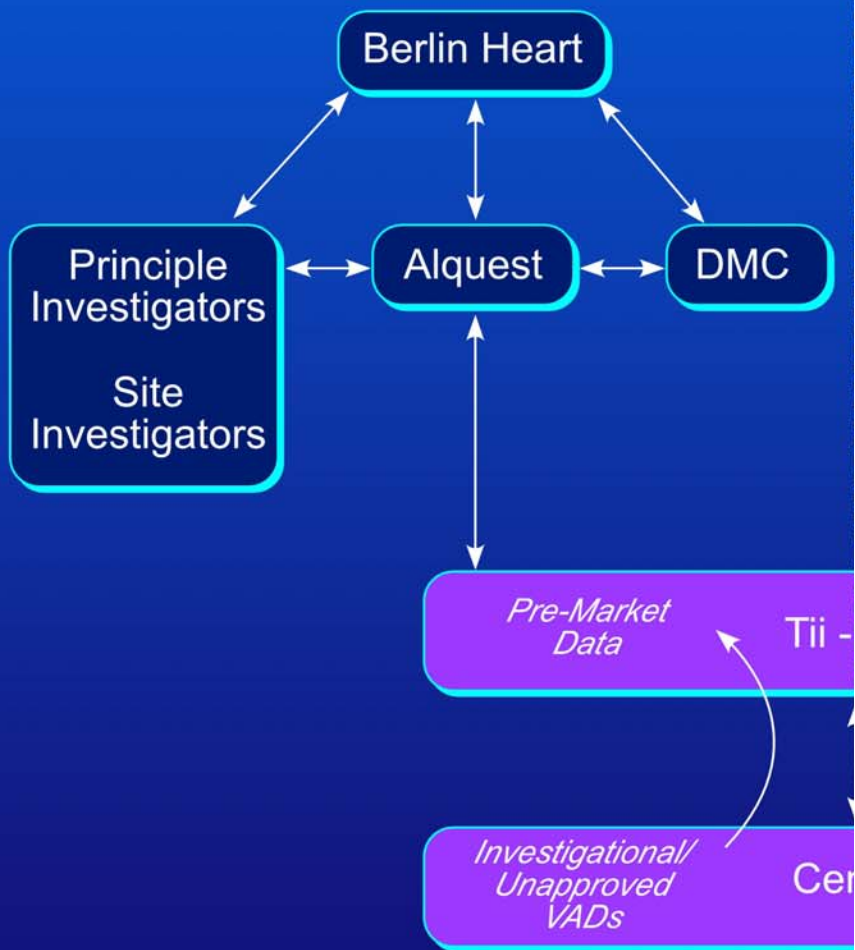
FDA – Food and Drug Administration  
 OSMB – Observational Safety Monitoring Board  
 UAB – University of Alabama at Birmingham

# Relationship Between Berlin Heart and INTERMACS

## INTERMACS



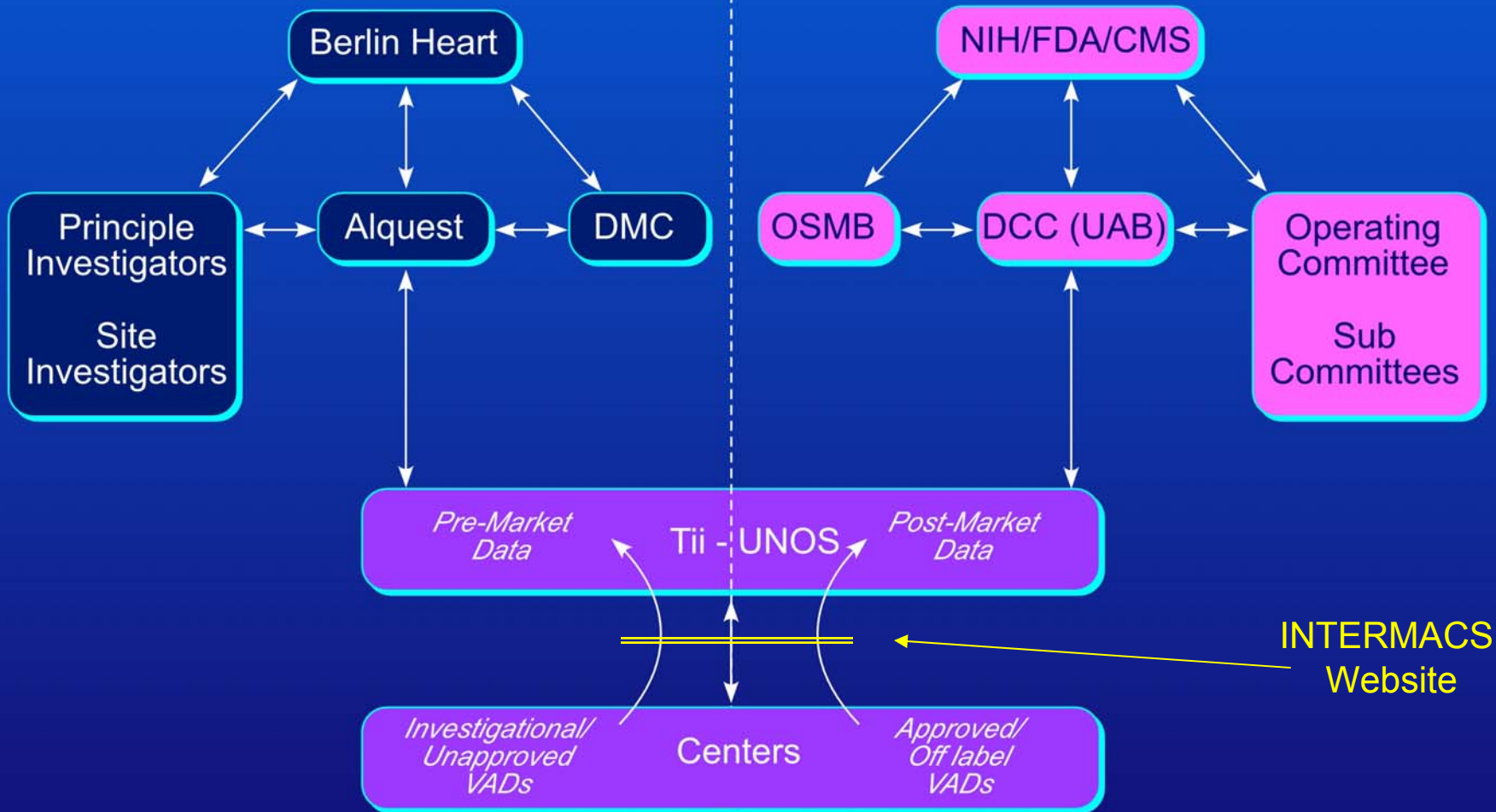
# BERLIN HEART





# BERLIN HEART

# INTERMACS



# Conclusions

---

- INTERMACS is rapidly emerging as a comprehensive data source on FDA-approved durable mechanical circulatory support devices, fulfilling its intended purpose
- The total number of pediatric patients enrolled in INTERMACS is small but growing and should increase significantly when more pediatric devices are FDA-approved
- INTERMACS is looking for ways to facilitate pre-market evaluation of pediatric devices and there are a number of potential strategies by which this can be achieved
- INTERMACS is poised to play a vital role in the evaluation of emerging pediatric VADs.