

**BERLIN HEART INC.**  
**HDE# H100004**

**Circulatory System Devices**  
**Advisory Panel**  
**Food and Drug Administration**  
**July 21, 2011**

**EXCOR® Pediatric**

# Company Overview

**Development, production and worldwide distribution of ventricular assist devices (VADs) for adult and pediatric populations**

- **Only company worldwide with VAD applications for patients with heart failure of every age and size**
- **Over 900 EXCOR® Pediatric implants worldwide**
- **Outside North America – Implantable INCOR® and EXCOR® adult and pediatric paracorporeal VAD**
- **United States – EXCOR® Pediatric paracorporeal VAD**



# Company Overview

- 1958** Prof. Emil Bucherl begins development of a circulatory assist device
- 1964** Research and development moved to German Institute
- 1978** EXCOR® Animal implants – Adult device
- 1984** First human implants EXCOR® Adult
- 1986** Berlin Heart GmbH Founded – development of EXCOR® Pediatric
- 1990** First Pediatric application
- 1996** EXCOR® System CE Mark Approval
- 1998** INCOR Design and development
- 2000** First US EXCOR® Pediatric Implant – CU Regulations
- 2002** First Human Implants INCOR
- 2005** Berlin Heart Inc. founded – FDA and Berlin Heart Inc. recognized the unmet clinical need - approval process begins
- 2007** IDE Approval – Study begins
- 2009** EXCOR® Pediatric Canadian Approval
- 2010** HDE Marketing application submitted

# Introduction

- **The EXCOR® Pediatric has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration under the Humanitarian Device Exemption (HDE) application H100004, which is the subject of this advisory panel meeting.**
- **The HDE application addresses the safety and probable benefit of the EXCOR® Pediatric in children at imminent risk of death from heart failure despite medical management.**

# Presenters

- **Charles D. Fraser, Jr., M.D., FACS\***  
Surgeon-in-Chief  
Clayton Chair in Surgery  
Donovan Chair and Chief, Congenital Heart Surgery / Texas Children's Hospital  
Professor of Surgery and Pediatrics / Baylor College of Medicine
  
- **Charles E. Canter, M.D.\***  
Medical Director, Heart Failure/Transplant Program, St. Louis Children's Hospital  
Professor of Pediatrics, Washington University School of Medicine
  
- **Mary Beth Kepler\*\***
- **Robert Kroslowitz\*\***
- **Christine Tjossem\*\***

***Disclosures:***

**\*No compensation from Berlin Heart Inc.**

**Institution reimbursed for costs associated with the conduct of the study**

**Travel expenses reimbursed by Berlin Heart Inc.**

**\*\*Employee of Berlin Heart Inc.**

# Expert Advisors

- **Christopher Almond, M.D.\***  
Children's Hospital Boston
- **Elaine Cox, M.D.**  
Riley Hospital for Children
- **Rebecca Ichord, M.D.\*\***  
Children's Hospital of Philadelphia
- **Tilman Humpl, M.D.**  
Hospital for Sick Children, Toronto
- **Robert Jaquiss, M.D.**  
Duke Children's Hospital
- **M. Patricia Massicotte, M.D.\*\***  
Stollery Children's Hospital
- **David Naftel, Ph.D.\*\*\***  
University Alabama-Birmingham
- **David Rosenthal, M.D.\*\***  
Lucile Packard Children's Hospital
- **James Tweddell, M.D.**  
Children's Hospital of Wisconsin
- **Peter Wearden, M.D.\*\***  
Pittsburgh Children's Hospital

## ***Disclosures:***

- No compensation from Berlin Heart Inc. for meeting attendance
- Travel expenses reimbursed by Berlin Heart Inc.
- Institution reimbursed for costs associated with the conduct of the study
- \* Dr. Almond is supported by Orphan Product Grant # 5RO1FD003557-03, which is associated with this study
- \*\*Clinical Event Committee Member
- \*\*\*Consultant

# **Charles D. Fraser, Jr., M.D., FACS**

**Surgeon-in-Chief**

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Texas Children's Hospital**

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# Intended Use

**EXCOR® Pediatric is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR® Pediatric.**

- **Transplant wait list mortality for children is high\***
- **Median wait time for heart transplant in children is 119 days\*\***

## References:

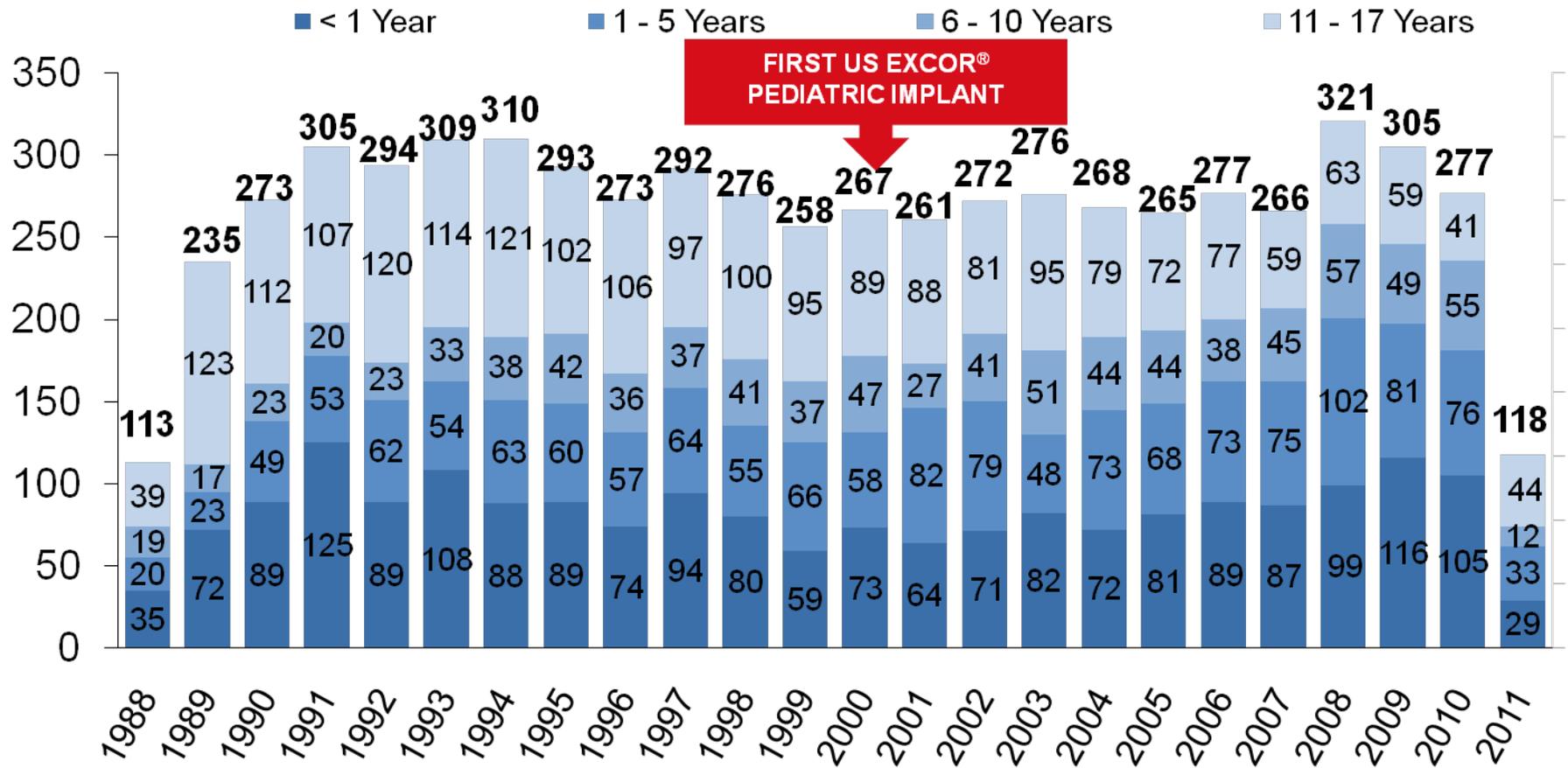
\* Almond CS, *Circulation* 2009: 199; 717-727

\*\* Larsen RL, 2011 *JHLT* 2011: 755-760

# Heart Failure in Children – Medical Need



## Annual Heart Transplants as reported by OPTN



# Heart Failure in Children – Options

- **Short-term Mechanical Circulatory Support:**
  - **ECMO or centrifugal VAD (Off label use)**
  
- **Long-term Mechanical Circulatory Support:**
  - **FDA Approved:**
    - **Adult VADs for children**
    - **DeBakey Child VAD (Not clinically adopted\*)**
  - **Clinical Trial: EXCOR® Pediatric VAD**

\*Reference: Fraser CD, Jr, *Seminars in thoracic and cardiovascular surgery*. 2006:109-114

# Heart Failure in Children – Options

## ADULT OPTIONS

### *FDA Approved Devices*

AbioCor TAH  
Novacor PC  
HeartMate IP  
Novacor PCq  
HeartMate VE  
Syncardia TAH  
HeartMate XVE  
Thoratec IVAD  
Thoratec PVAD  
HeartMate II

### *Investigational Devices*

Jarvik 2000  
MicroMed DeBakey  
Evaheart  
Terumo Duraheart  
Heartware  
Levacor

## CHILD OPTIONS

### *FDA Approved Devices*

MicroMed DeBakey-Child

### *Investigational Devices*

EXCOR® Pediatric

# Heart Failure in Children – Options



# EXCOR® Device Description

## Paracorporeal ventricular assist device (VAD)



IKUS® driving unit

# EXCOR<sup>®</sup> Device Description

- Uni - or Bi- Ventricular Support
- Longest application > 1000 days
- Wide selection of blood pumps and cannulas
- Specially designed small pumps and cannulas for infants and children
- Easy visual inspection of the blood pumps (pump performance and/or deposit formation)
- Paracorporeal design allows for ease of exchange due to upsize or thrombus



# Selection of Blood Pump Size

- Based on weight
- For BVAD larger pump size on the left
- For BVAD use combination of 10/10 ml, 25/30 ml, 50/60 ml

## LVAD

Body weight	Pump size
up to 9 kg	10 ml
9 kg to 25 kg	25 ml
15 kg to 30 kg	30 ml
30 kg to 55 kg	50 ml
35 kg to 60 kg	60 ml

## BVAD

Bodyweight	Pump size L/R
Up to 9 kg	10 / 10 ml
9 kg to 30 kg	30 / 25 ml
30 kg to 60 kg	60 / 50 ml



# Pump Change Process

- Easy to prime and de-air the pump
- Change does not require general anesthesia or surgical intervention
- No substantive interruption of mechanical support
- Bedside procedure

# EXCOR® Pediatric Cannulas

- Wide selection of different sizes, head angles and diameters
- Coated with velour to promote good ingrowth and prevent ascending infection



**Atrial**



**Apical**



**Arterial**

# EXCOR® Ikus Driving Unit

- **Electro pneumatic driving unit**
- **Suitable for all EXCOR® blood pumps**
- **Uni- and biventricular operation**
- **Battery back-up**
- **Hand pump provided for emergency use**
- **Various operating modes for BVAD support**



Group	Total Implants
U.S. Pre IDE Approval (2000-2007)	97
IDE Primary Study Cohorts	48*
IDE Continued Access	20
Compassionate Use IDE Sites	41
Compassionate Use Non-IDE Sites	95
<b>Total</b>	<b>301</b>

**\*Primary analysis group (n=48)**

## ***EFFICACY***

**The primary objective of the study was to demonstrate that the survival rate in subjects treated with the EXCOR® Pediatric was different from the survival rate in the historical control of subjects treated with ECMO as a bridge to cardiac transplant.**

**Survival time is defined by the interval of time from initiation of mechanical support to an endpoint (cardiac transplantation, death or recovery, where recovery is the longer of hospital discharge or 30 days post-explant)**

## ***SAFETY***

**The primary objective of the study was to summarize the serious adverse event (SAE) rate calculated as the number of serious adverse events per patient-day of support on EXCOR® Pediatric.**

# Study Oversight: Clinical Events Committee



NAME	AFFILIATION	EXPERTISE
M. Patricia Massicotte, M.D. FRCPC MHSc <i>Committee Chair</i>	Stollery Children's Hospital	Pediatric Thrombosis
Francisco Arabia, M.D.	Mayo Clinic	Adult Cardiac Surgery
Daphne Hsu, M.D.	Children's Hospital at Montefiore	Pediatric Cardiology
Rebecca Ichord, M.D.	Children's Hospital of Philadelphia	Pediatric Neurology
Lori Jordan, M.D.	The John's Hopkins University School of Medicine	Pediatric Neurology
Leslie Raffini, M.D.	Children's Hospital of Philadelphia	Pediatric Thrombosis
David Rosenthal, M.D.	Lucile Packard Children's Hospital	Pediatric Cardiology
Robert Shaddy, M.D.	Children's Hospital of Philadelphia	Pediatric Cardiology
Peter Wearden, M.D., PhD	Children's Hospital of Pittsburgh	Pediatric Cardiac Surgery

# Study Oversight: Data Monitoring Committee Berlin Heart®

<b>NAME</b>	<b>AFFILIATION</b>	<b>EXPERTISE</b>
Douglas Hawkins, PhD <i>Committee Chair</i>	Douglas Hawkins LLC University of Minnesota	Biostatistician
Michèle David, M.D.	Hôpital Sainte-Justine	Pediatric Hematology/ Thrombosis
Heather J. Fullerton, M.D., MAS	University of California, San Francisco	Pediatric Neurology
Beth Kaufman, M.D.	Children's Hospital of Philadelphia	Pediatric Cardiology, Heart Failure & Heart Transplant
Peter Manning, M.D.	Cincinnati Children's Hospital Medical Center	Pediatric Cardiothoracic Surgery

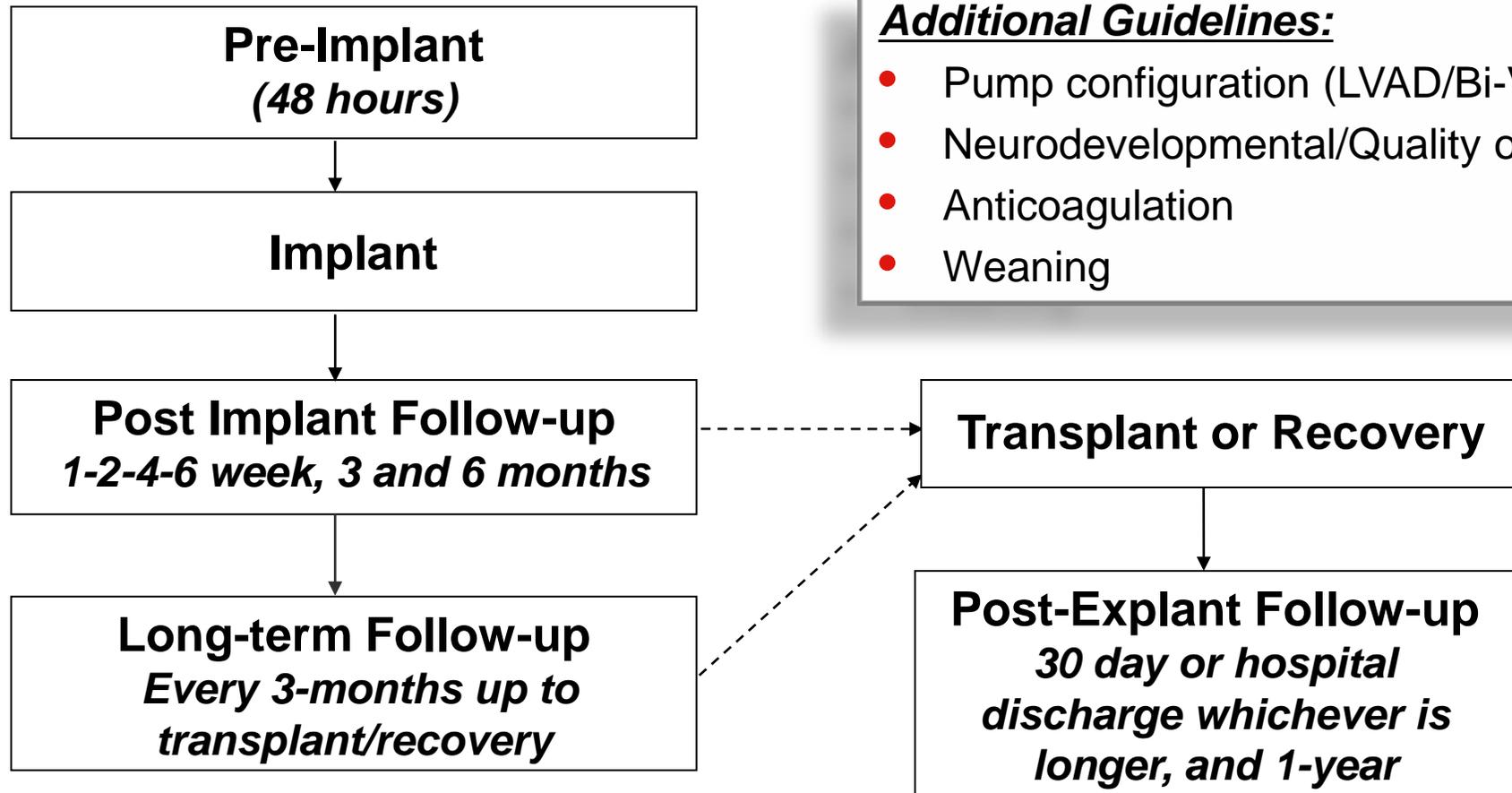
## *Inclusion Criteria:*

- Severe heart failure refractory to optimal medical therapy (NYHA Functional Class IV or Ross Functional Class IV for subjects  $\leq 6$  years) and has met at least one of the following criteria:
  - INTERMACS Patient Profile status 1 or 2  
or Pre-Implant ECMO or VAD  
or Failure to Wean from bypass
- Listed for cardiac transplantation
- Two-Ventricle circulation
- Age 0 – 16 years
- Weight 3-60 kg

## *Exclusion Criteria:*

- Supported on ECMO  $\geq$  10 days
- CPR  $\geq$  30 minutes
- Mechanical Aortic Valve
- Complex congenital or unfavorable anatomy
- Irreversible end-organ dysfunction
- Documented HIT or coagulation disorder
- Active infection
- Life-limiting disease
- Stroke within 30 days or congenital CNS with risk of bleeding

# IDE Study Design: Follow-up Schedule



# IDE Study Design: Description of Cohorts

Study Population	N	Description
<b>STUDY COHORTS (SUPPORT SAFETY AND EFFECTIVENESS)</b>		
Cohort 1	24	Children with smaller BSA up to 0.7 m <sup>2</sup>
Cohort 2	24	Children with larger BSA $\geq 0.7$ m <sup>2</sup> to $<1.5$ m <sup>2</sup>
<b>ADDITIONAL COHORTS (SUPPORT SAFETY)</b>		
Compassionate Use	136	Did not meet eligibility criteria at IDE sites or were implanted at a Non-IDE site
Continued Access	20	Extension for subjects meeting entrance criteria

# **Charles E. Canter, M.D.**

**Medical Director, Heart Failure/Transplant Program, St.  
Louis Children's Hospital  
Professor of Pediatrics, Washington University School  
of Medicine**

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- **Developed from Extracorporeal Life Support Organization (ELSO) Registry database**
- **Only available multi-center control group dataset**
- **Developed in coordination with FDA**

# IDE Study Design: Historical Control

## Limitations of ELSO database:

- **Voluntary registry** (no mandatory reporting requirements)
- **Adverse Events not clearly defined** (and do not match IDE trial / INTERMACS)
- **Unadjudicated SAEs**
- **Incomplete outcomes data**
  - **Limited to mortality (lacks transplant/recovery)**
  - **Limited discharge information**
  - **On/Off ECMO**
- **Unmonitored data collection**

## Database was filtered to match IDE population:

- Age 0-16 years
- Weight >3 kg
- Cardiac only ECMO
- Support from 2000 to 2007
- Removed complex congenital and trauma

- **Propensity Score Analysis was used to create the control group used for the Primary Effectiveness Endpoint analysis**
- **Propensity score is the conditional probability of receiving an EXCOR® rather than ECMO using the following variables:**
  - Age, Weight, Diagnosis, Ventilator status, Inotrope use, and Prior cardiac arrest*
- **Each EXCOR® subject matched to 2 ELSO controls based on propensity score**

# IDE Study Design: PSA Results Cohort 1

Variable	Category	Cohort 1 N=24	ELSO Matched Group N=48	P-value
<b>Age</b> (months)	Mean ± Std	15.4 ± 12.4	18.5 ± 11.5	0.29
	Median	11.7	16.1	
	Min – Max	2.6 - 45.6	1.8 – 43.7	
<b>Weight</b> (kg)	Mean ± Std	9.1 ± 2.7	9.4 ± 2.4	0.64
	Median	9.2	9.9	
	Min - Max	3.6 - 13.6	4.0 - 13.9	
<b>Primary Diagnosis</b>	Congenital Heart Disease	3 (12.5%)	9 (18.8%)	0.31
	Coronary Artery Disease	0 ( 0.0%)	0 ( 0.0%)	
	Dilated Cardiomyopathy	19 (79.2%)	38 (79.2%)	
	Hypertrophic Cardiomyopathy	1 ( 4.2%)	0 ( 0.0%)	
	Restrictive Cardiomyopathy	1 ( 4.2%)	0 ( 0.0%)	
	Valvular Heart Disease	0 ( 0.0%)	1 ( 2.1%)	

# IDE Study Design: PSA Results Cohort 1

<b>Variable</b>	<b>Cohort 1 N=24</b>	<b>ELSO Matched Group N=48</b>	<b>P-value</b>
<b>Ventilator Use Pre-implant</b>	20 (83.3%)	42 (87.5%)	0.72
<b>Inotrope Use Pre-implant</b>	22 (91.7%)	45 (93.8%)	1.00
<b>Cardiac Arrest Pre-implant</b>	7 (29.2%)	15 (31.3%)	1.00

# IDE Study Design: PSA Results Cohort 2

Variable	Category	Cohort 2 N=24	ELSO Matched Group N=48	P-value
<b>Age</b> (months)	Mean ± Std	113.2 ± 37.6	117.0 ± 44.3	0.72
	Median	111.2	118.5	
	Min – Max	50.8 - 191.8	50.2 – 188.6	
<b>Weight</b> (kg)	Mean ± Std	32.2 ± 12.5	31.7 ± 13.3	0.88
	Median	30.7	27.0	
	Min – Max	16.0 – 58.1	13.0 – 59.0	
<b>Primary Diagnosis</b>	Congenital Heart Disease	6 (25.0%)	17 ( 35.4%)	0.50
	Coronary Artery Disease	0 ( 0.0%)	1 ( 2.1%)	
	Dilated Cardiomyopathy	17 (70.8%)	29 (60.4%)	
	Hypertrophic Cardiomyopathy	0 ( 0.0%)	0 ( 0.0%)	
	Restrictive Cardiomyopathy	1 ( 4.2%)	0 ( 0.0%)	
	Valvular Heart Disease	0 ( 0.0%)	0 ( 0.0%)	

# IDE Study Design: PSA Results Cohort 2

<b>Variable</b>	<b>Cohort 2 N=24</b>	<b>ELSO Matched Group N=48</b>	<b>P-value</b>
<b>Ventilator Use Pre-implant</b>	11 (45.8%)	30 (62.5%)	0.32
<b>Inotrope Use Pre-implant</b>	21 (87.5%)	44 (91.7%)	0.68
<b>Cardiac Arrest Pre-implant</b>	5 (20.8%)	15 (31.3%)	0.41

- **Control group constructed that is comparable based on several measured critical clinical variables**
- **Possible that there are unmeasured clinical variables and variation in clinical site experience and care protocols**
- **Experience in ELSO registry represents reasonable reference group**

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**Surgeon-in-Chief**

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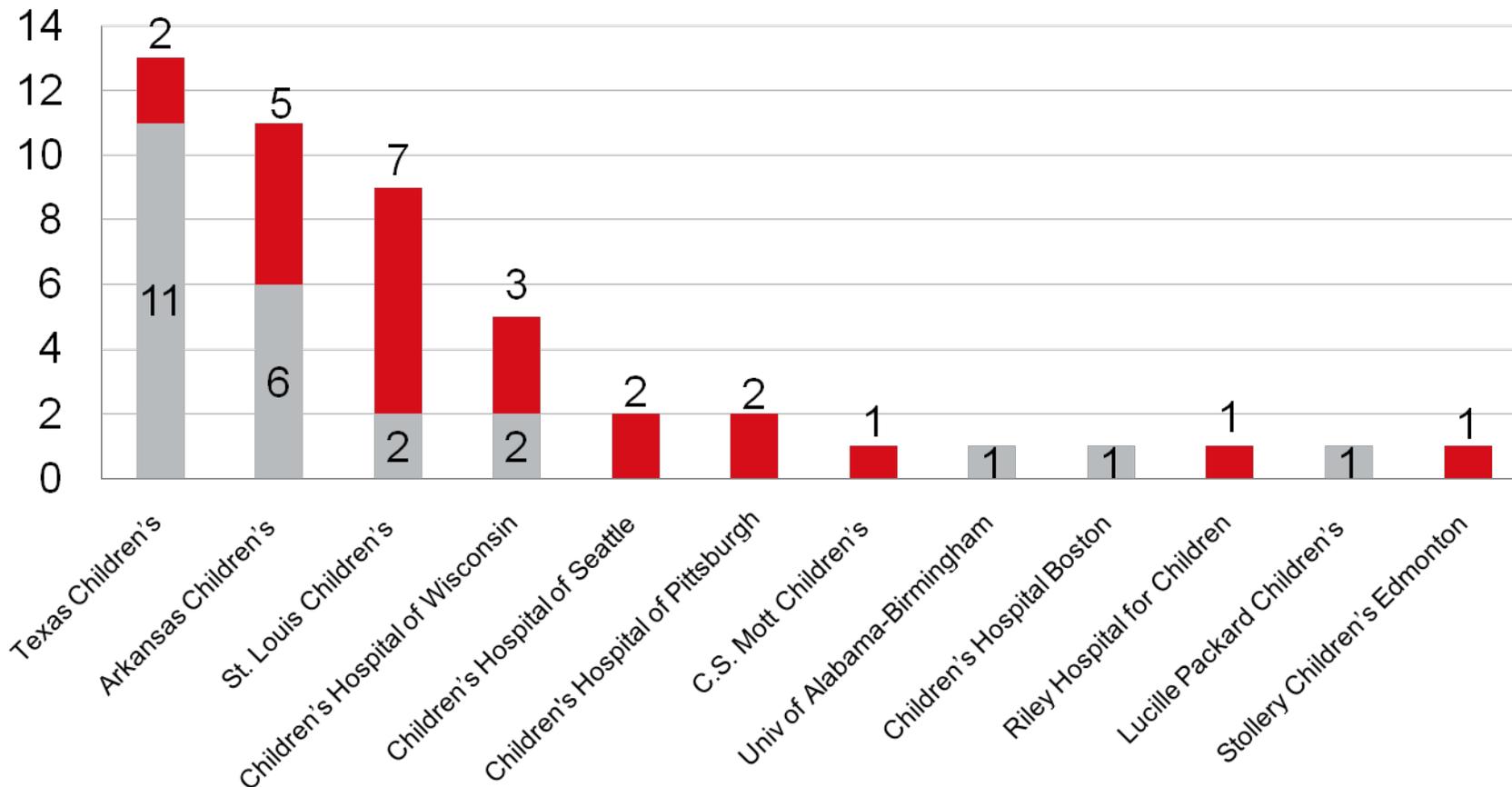
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# Study Implementation: Site Enrollment

- Cohort 1 n=24 implanted 12/14/07 to 08/18/09
- Cohort 2 n=24 implanted 11/28/07 to 08/26/10



**The primary objective of the study was to demonstrate that the survival rate in subjects treated with the EXCOR® Pediatric was different from the survival rate in the historical control of subjects treated with ECMO as a bridge to cardiac transplant**

## *Hypotheses:*

$H_0$ : EXCOR® Survival = ECMO Survival

$H_A$ : EXCOR® Survival  $\neq$  ECMO Survival

## *Statistical Methods:*

Estimation: Kaplan-Meier method

Test of significance: log-rank test

## ***“Death” (failure)***

- Death on EXCOR/ECMO prior to transplant
- Weaned off EXCOR/ECMO and died within 30 days or prior to discharge (whichever is longer)
- Weaned off EXCOR with unacceptable neurological outcome\* within 30 days or prior to discharge (whichever is longer)

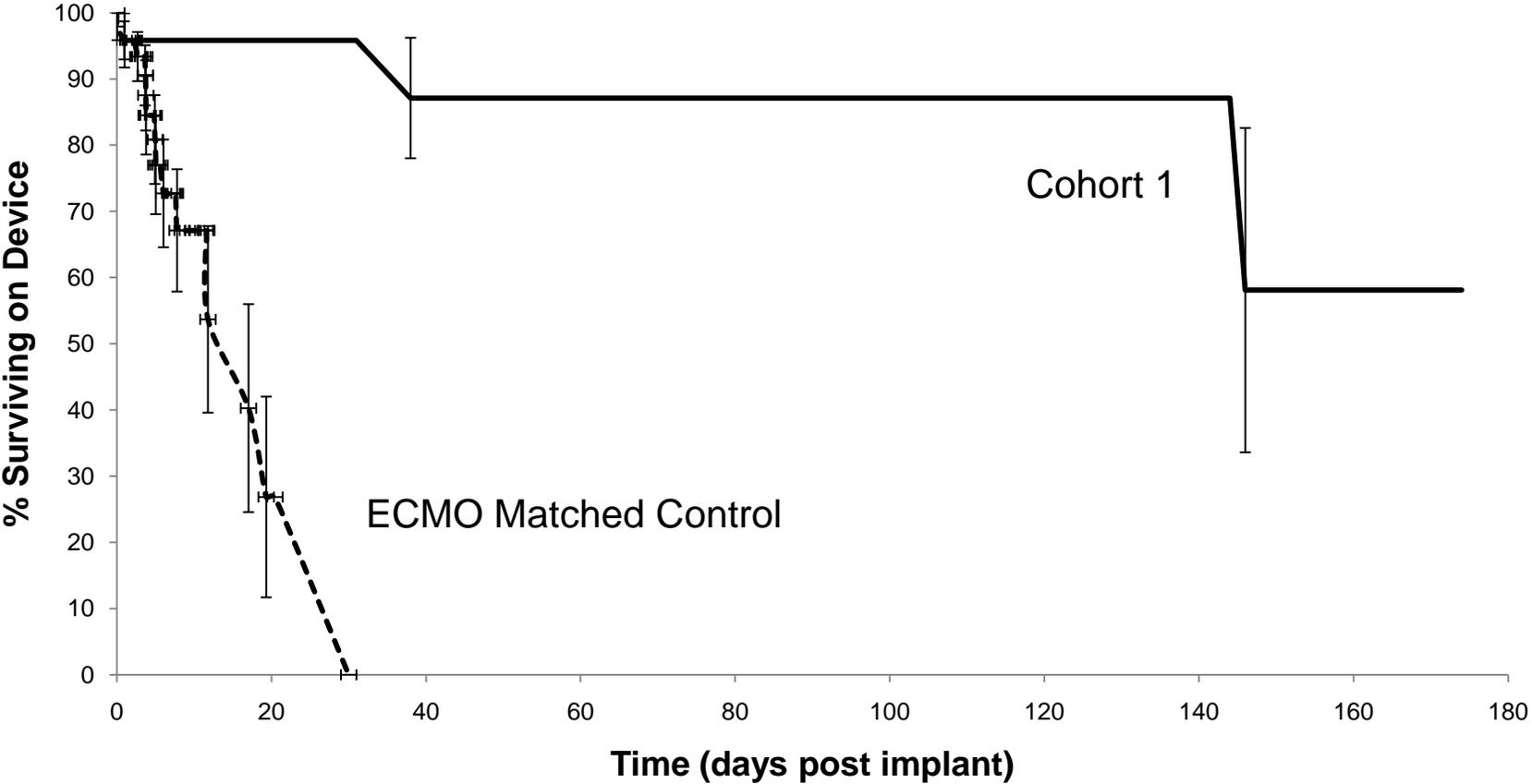
## ***“Alive” (censored)***

- Transplanted (deaths post transplant are not counted)
- Weaned due to recovery and survives to discharge or 30 days (censored at time of weaning)

***\*neurological status not available for ELSO subjects after removal from ECMO***

# Trial Results: Effectiveness Endpoint

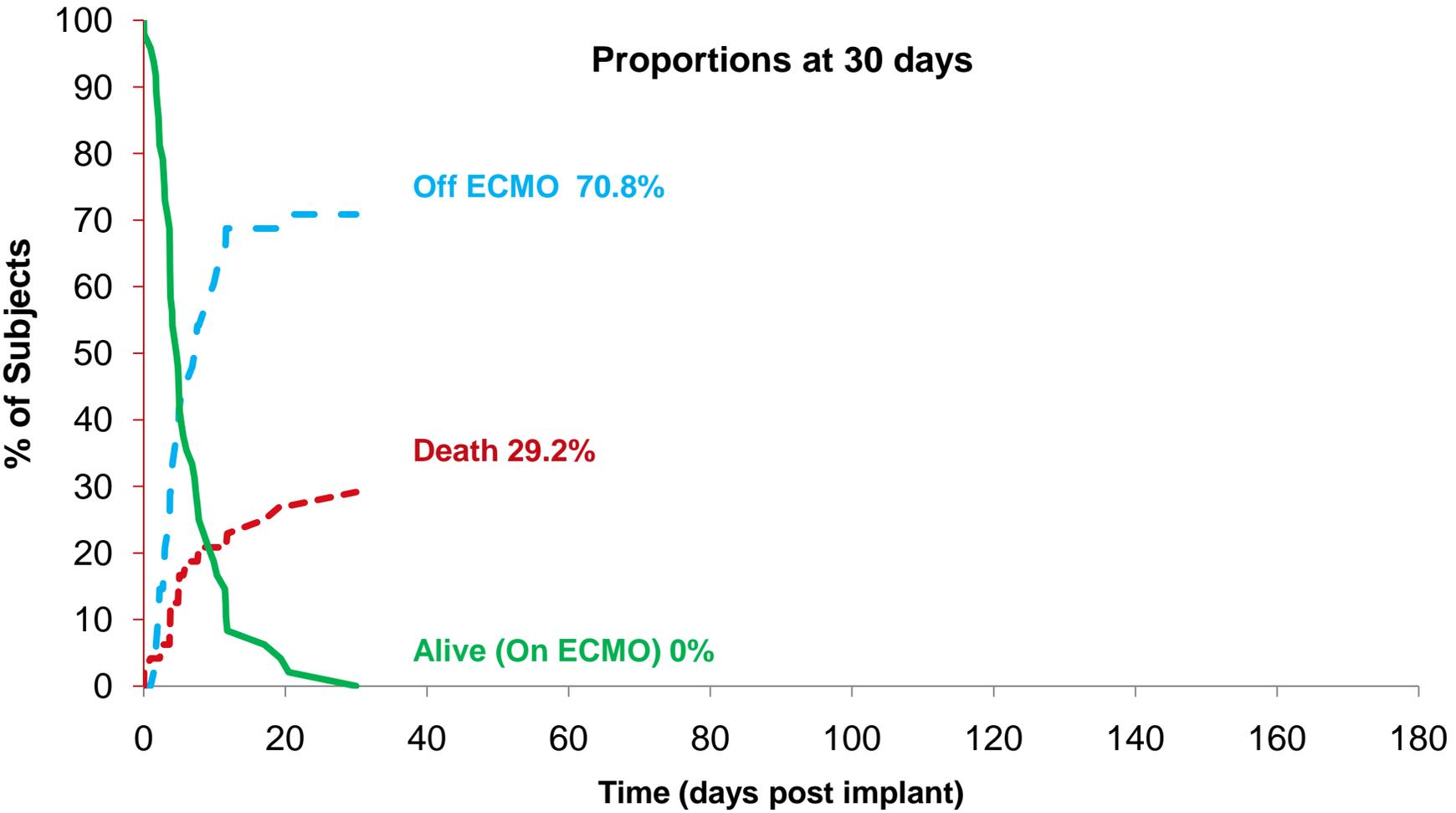
Survival Analysis where Event =  
Death/ Weaned with Unacceptable Neuro Outcome  
(censored at Transplant and at Recovery)



Log rank p-value  $p < 0.0001$

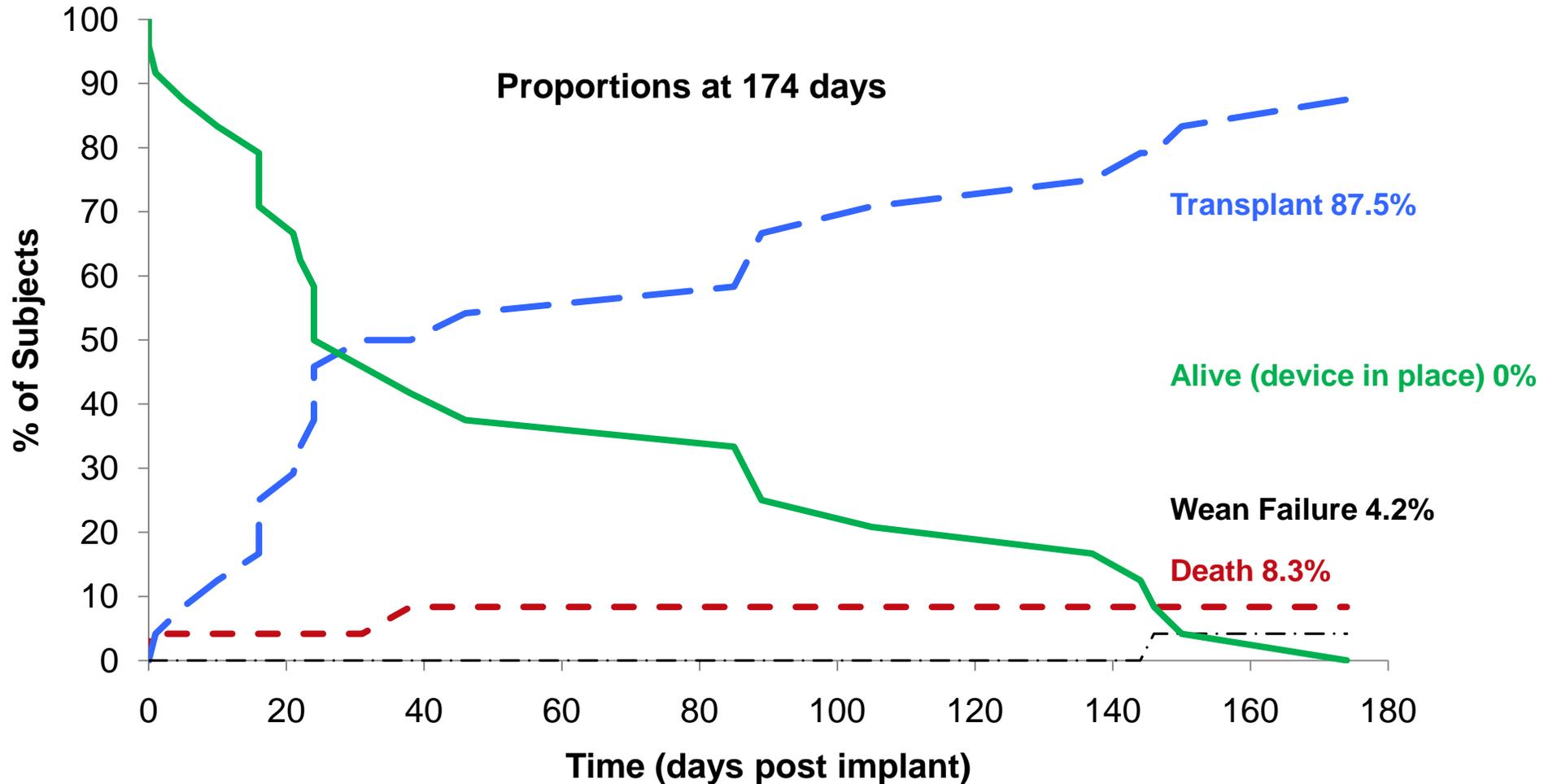
# Trial Results: Effectiveness Endpoint

## ECMO Control Group for Cohort 1 - Competing Outcomes



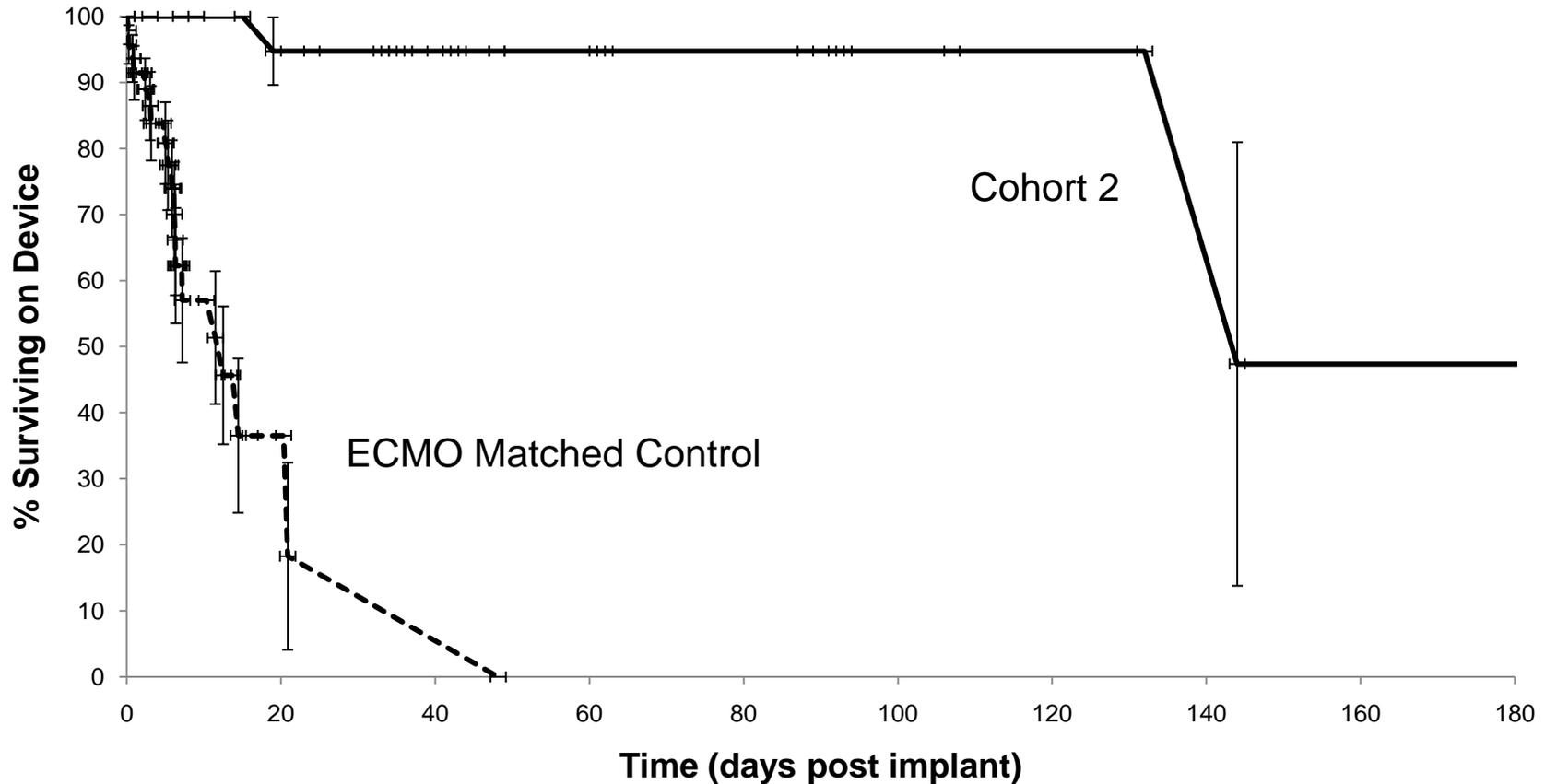
# Trial Results: Effectiveness Endpoint

## Cohort 1 - Competing Outcomes



# Trial Results: Effectiveness Endpoint

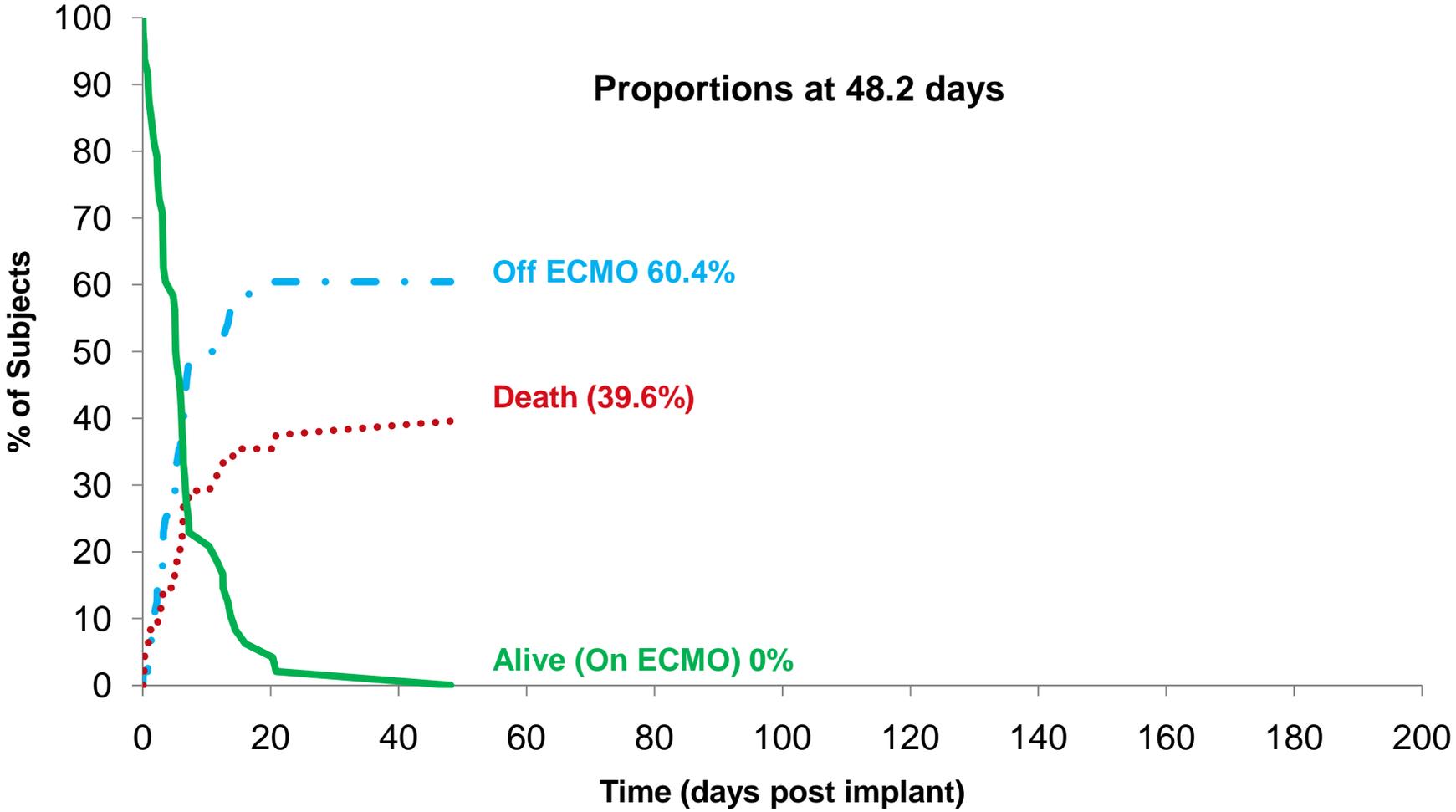
Survival Analysis where Event =  
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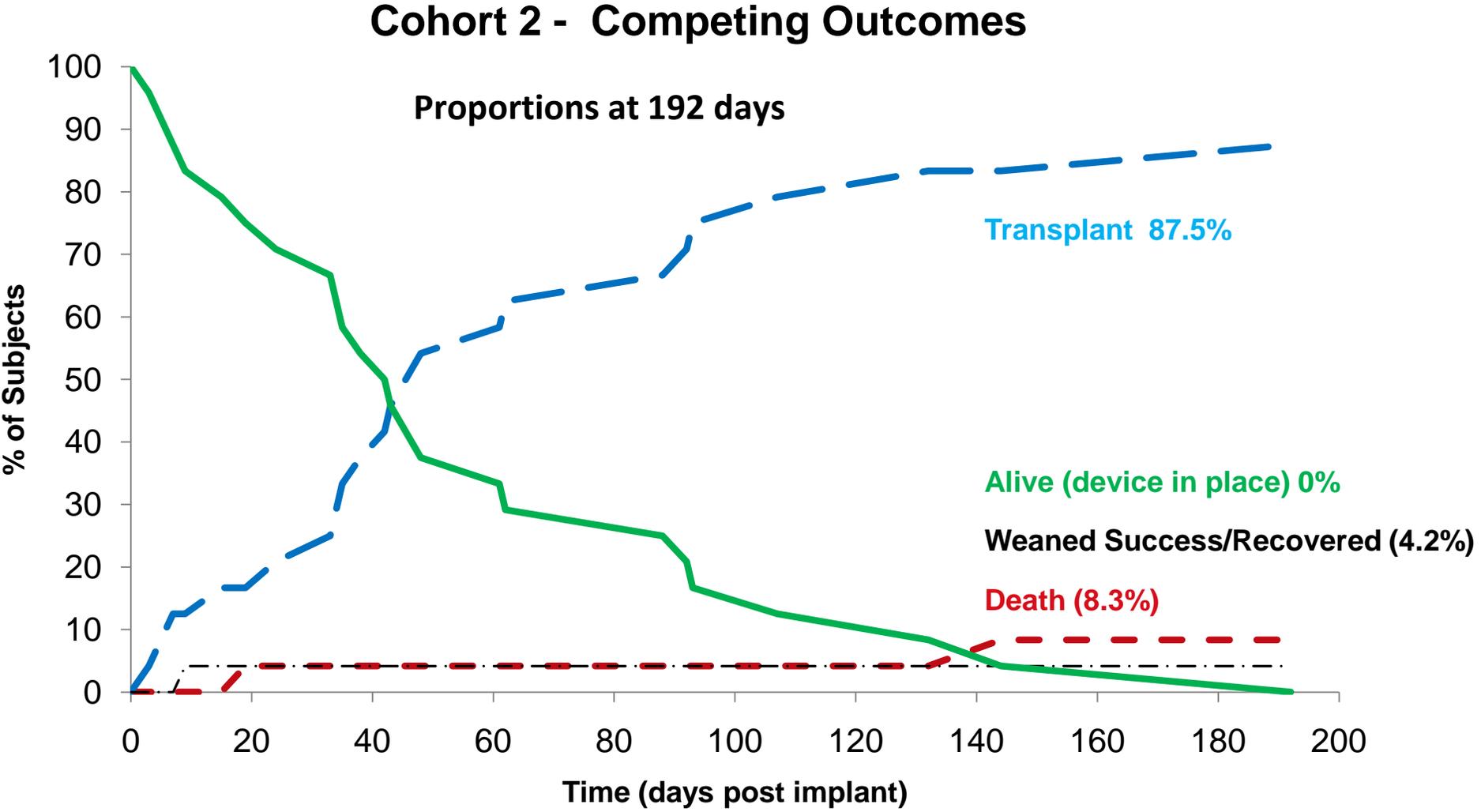
Log rank p-value  $p < 0.0001$

# Trial Results: Effectiveness Endpoint

## ECMO Control Group for Cohort 2 - Competing Outcomes



# Trial Results: Effectiveness Endpoint



# Trial Results: Outcomes

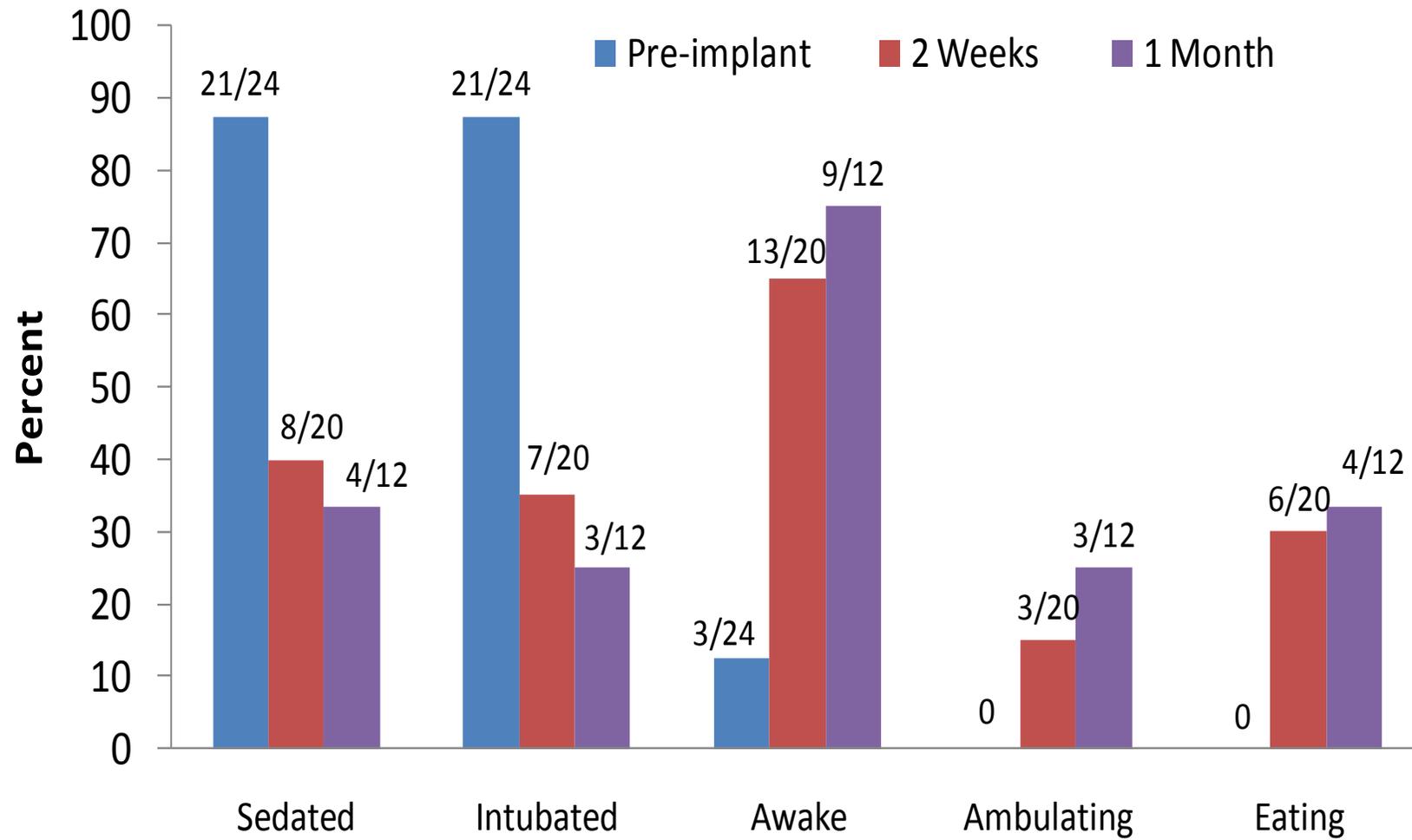
Group	N	Outcome				Success*
		Tx	Off Device Recovered	Off Device Failure	Died	
Cohort 1	24	21	0	1	2	21 (87.5%)
ELSO Matched Control	48		34	8	6	34 (70.8%)
Test for differences in success rate at 30 days Cohort 1 (96%) versus ELSO (77%) p=0.05 (Chi-square)						
Cohort 2	24	21	1	0	2	22 (91.7%)
ELSO Matched Control	48		29	11	8	29 (60.4%)
Test for differences in success rate at 30 days Cohort 2 (96%) versus ELSO (71%) p=0.01 (Chi-square)						

*\*Success Definitions:*

*EXCOR Transplanted or Weaned off device with acceptable neuro outcome within 30 days/discharge*

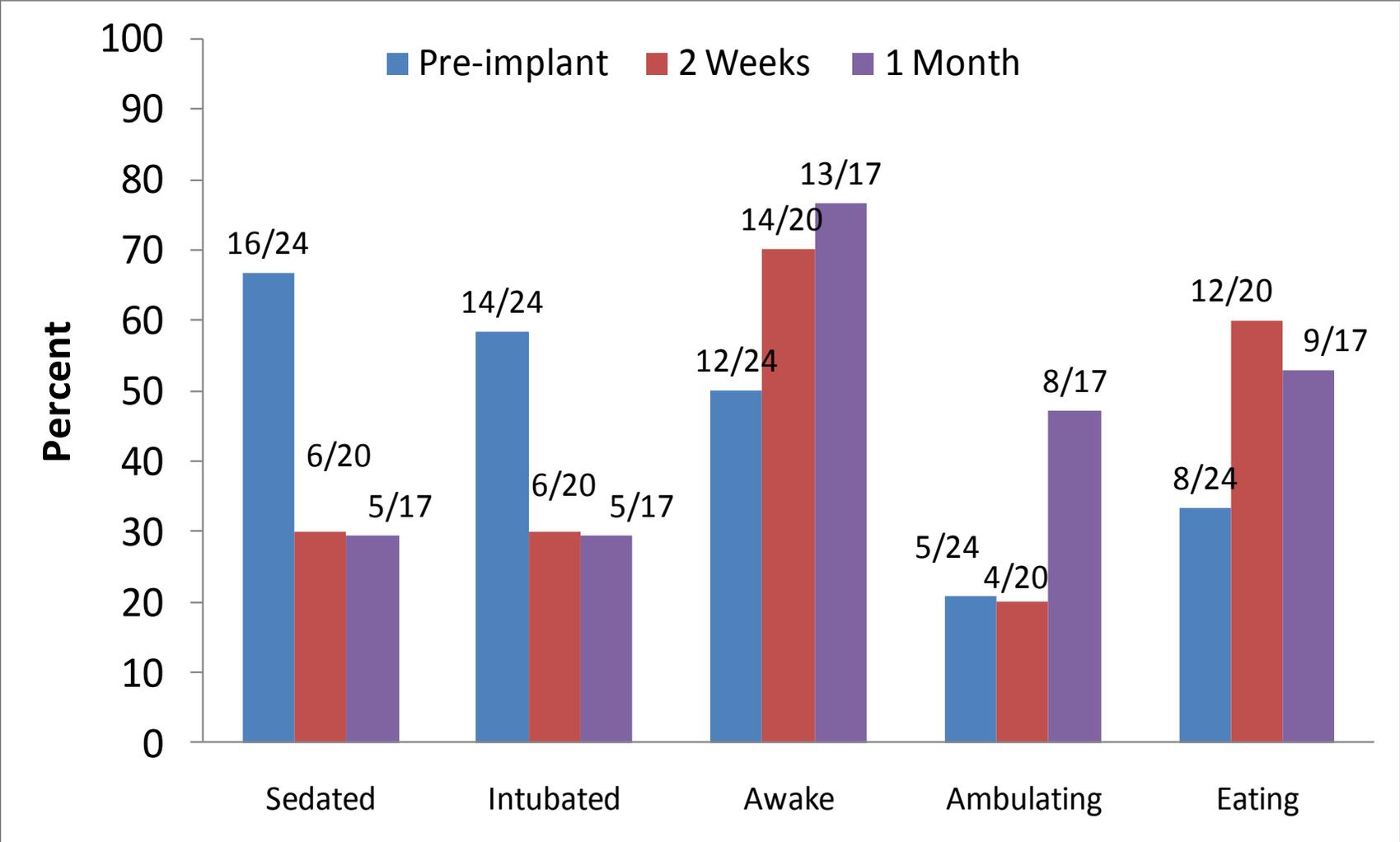
*ELSO Removed from ECMO (incomplete discharge status data and no transplant information available)*

# Trial Results: Cohort 1 Patient Status



**Note: median age of this cohort is 12 months**

# Trial Results: Cohort 2 Patient Status



# Trial Results: Patient Status



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# Trial Results: Safety Endpoint

- No greater than 0.25 events per patient-day were expected during the time the subject was on support
  - 0.25 events/patient-day was derived from historical US experience (2000-2007) and in coordination with FDA during study protocol development
- All SAEs for patients implanted at IDE sites were adjudicated
- SAE were defined according to INTERMACS criteria

## *Hypotheses:*

$H_0$ : EXCOR® SAE Rate  $\geq 0.25$

$H_A$ : EXCOR® SAE Rate  $< 0.25$

## *Statistical Methods:*

Estimation: SAE rate (total number events/total support time)

Test of significance: Upper CI of Poisson Confidence Interval

# Trial Results: Safety Endpoint

Cohort	N	# Total SAEs	Total time On support (Days)	Rate Per patient-day	Upper Bound 95% CI
1	24	96	1411	0.068	0.083
2	24	107	1376	0.078	0.094

Poisson Estimate and Upper Confidence Interval (CI)

# Trial Results: Safety for ECMO Prior

Cohort	ECMO Pre	N	# Total SAEs	Total time on support (Days)	Rate Per patient-day	Upper Bound 95% CI
1	No	18	58	1066	0.054	0.070
	Yes	6	38	345	0.110	0.151
2	No	16	64	926	0.069	0.088
	Yes	8	43	450	0.096	0.129

Poisson Estimate and Upper Confidence Interval (CI)

# Trial Results: Serious Adverse Events

SAE	Cohort 1		Cohort 2	
	# events	# (%) with an Event	# events	# (%) with an Event
Major Bleeding	15	10 (41.7%)	22	12 (50.0%)
Infection-Localized Non-Device	25	12 (50.0%)	18	10 (41.7%)
Infection-Site or Pocket	4	4 (16.7%)	0	0 ( 0.0%)
Infection-Sepsis	6	5 (20.8%)	6	6 (25.0%)
Neurological Dysfunction	8	7 (29.2%)	9	7 (29.2%)
Ischemic	8		7	
Hemorrhagic	0		2	
Hypertension	12	12 (50.0%)	8	8 (33.3%)
Respiratory Failure	3	3 (12.5%)	9	6 (25.0%)
Cardiac Arrhythmia-Sustained VT	1	1 ( 4.2%)	2	2 ( 8.3%)
Cardiac Arrhythmia-Sustained SVT	0	0 ( 0.0%)	4	3 (12.5%)

# Trial Results: Serious Adverse Events

SAE	Cohort 1		Cohort 2	
	# events	# (%) with an Event	# events	# (%) with an Event
Pericardial Fluid -W/Tamponade	1	1 ( 4.2%)	2	2 ( 8.3%)
Pericardial Fluid -W/out Tamponade	2	2 ( 8.3%)	2	2 ( 8.3%)
Renal Dysfunction-Acute	3	2 ( 8.3%)	2	2 ( 8.3%)
Right Heart Failure	2	2 ( 8.3%)	3	3 (12.5%)
Hemolysis-Late	1	1 ( 4.2%)	1	1 ( 4.2%)
Hepatic Dysfunction	1	1 ( 4.2%)	1	1 ( 4.2%)
Psychiatric Episode	0	0 ( 0.0%)	1	1 ( 4.2%)
Renal Dysfunction-Chronic	0	0 ( 0.0%)	2	2 ( 8.3%)
Arterial Non-CNS Thromboembolism	1	1 ( 4.2%)	0	0 ( 0.0%)
Venous Thromboembolism Event	1	1 ( 4.2%)	0	0 ( 0.0%)
Other	10	6 (25.0%)	15	6 (25.0%)
Device Malfunction	0	0 ( 0.0%)	0	0 ( 0.0%)

- Anticoagulation guidelines incorporated agents:
  - Unfractionated heparin, low molecular weight heparin, warfarin, dipyridamole and aspirin
- Centers were adherent to recommended anticoagulation guidelines as indicated by the means of the primary laboratory tests used to monitor anticoagulation
- Neurological dysfunction, bleeding events and pump changes were not related to the intensity of anticoagulation

# Trial Results: Bleeding SAEs

- Major Bleeding occurred in 46% (22/48) of patients
  - If on ECMO prior: 62% ( 8/13)
  - If not on ECMO prior: 40% (14/35)
- Median time to Major Bleeding 4.5 days
  - 37 bleeding events in 22 patients
    - 10 patients had 1 event
    - 12 patients had more than 1 event
- Only 9 of 37 events involved reoperation
- No bleeding-related deaths

# Trial Results: Infection SAEs

- **Major Infection occurred in 56% (27/48) of patients**
  - Localized Non-Device occurred in 46% (22/48) patients
  - Site or Pocket occurred in 8% (4/48) patients
  - Sepsis occurred in 23% (11/48) patients
- Infection SAEs appear to be related to issues of medical management of the critically ill child and associated instrumentation violating host defenses rather than to implantation or use of the device
- No deaths were attributable to infection and there was no time patients were considered inactive for transplant due to infection
- Only 1 of the reported infectious SAEs could be attributed to use of the device
  - Drive line exit site irritation that resulted in breakdown of skin, colonization and then infection with *pseudomonas aeruginosa*

- **Neurological Dysfunction occurred in 29% (14/48) of patients**
  - Ischemic CVA occurred in 29% (14/48) of patients
  - Hemorrhagic CVA occurred in 4% (2/48) patients
- **Neurologic Event Ascertainment:**

PSOM used to record & rate exam findings

  - Rigorous monitoring of neurologic status at pre-implantation and while on device (1 week, 1 month, 3 months, every 3 months)
  - Standard clinical assessment for overt neurologic symptoms by neurology consultants per local institution standards
- **Neurologic Event Adjudication:**

CEC review of clinical records & CT findings; classification of neuro event type & relationship to device
- **Caveats, limitations:**

ECMO control group lacked similar systematic neuro evals; PSOM scores < 6 month post explant likely not accurate reflection of true long-term outcome; many factors besides stroke or device exposure affect outcome

- **Use of PSOM in this trial:**
  - Exam recording tool & rating method to classify the findings of a typical standard complete neurological examination performed by a child neurologist
  - Final summary score ranges 0-10 (normal-abnormal)
  
- **Stratification of PSOM scores used in this trial\***
  - 0 = normal
  - 0.5 or 1.0 = mild deficit
  - 1.5 or 2.0 = moderate deficit
  - ≥2.5 = severe deficit

\*Supported by data reported in Beslow et al *Stroke* 2010, 41:313-318

# Trial Results: Cohort 1 Neurological Status

ID	Neuro Days Post Implant	PSOM At time of event	Highest PSOM Reported	Latest PSOM	PSOM Category	Latest Verbal Report
007-101	20 d	0.5 (7 d)	1.5 (pre)	0.0 (17 post tx)	No Deficit	Doing well from Cardiac status 970 days post explant
006-102	15 d	Unable (7 d)	7.0 (5 post tx)	1.0 (221 post tx)	Mild 0.5-1.0	Alive, Delayed, speech and OT therapy 1157 days post explant
010-106	60 d	3.0 (31 d)	6.0 (pre)	0.5 (23 post tx)	Mild 0.5-1.0	Doing fabulous, riding horses 571 days post explant
004-101	37 d	4.5 (31 d)	5 (19 d)	1.5 (82 post tx)	Mod 1.5-2.0	Survived 341 days post transplant then expired
004-105	13 d	Unable (13 d)	3.5 (90 d)	3.0 (34 post tx)	Severe > 2.0	Doing well, no focal deficits 630 days post explant
006-105	20 d	Unable (14 d)	10 (20 post tx)	4.0 (54 post tx)	Severe > 2.0	Survived 181 days post transplant then died from mudden cardiac death
008-101	26 d	Unable (8 d)	Unable	N/A	N/A	Withdrawn from support

# Trial Results: Cohort 2 Neurological Status

ID	Neuro Days Post Implant	PSOM At time of event	Highest PSOM Reported	Latest PSOM	PSOM Category	Latest Verbal Report
006-101	1 d	Unable (pre)	0.5 (30 d)	0.0 (50 post tx)	No Deficit	Survived 419 days post transplant then expired.
006-104	6 d	0.0 (pre)	6.0 (37 d)	0.5 (49 post tx)	Mild 0.5-1.0	Awake, alert and eating, receives physical, occupational and speech therapy [08/18/08] 49 days post explant
007-107	8 d	Unable (pre)	5.0 (9 d)	1.0 (27 post tx)	Mild 0.5-1.0	Wechsler evaluation average IQ; currently uses left hand to write, increased strength in right hand [04/27/11] 393 days post explant
009-101	14 d	Unable (14 d)	6.0 (80 d)	2.0 (357 post tx)	Mod 1.5-2.0	Overall been well since transplant; residual neurologic abnormalities with hypertonic left leg; cheerful, interactive, and attends school full-time [04/01/11] 947 days post explant
006-111	12 d	Unable (12 d)	10 (29 post tx)	10 (29 post tx)	Severe > 2.0	Multiple residual problems: non verbal with right-sided hemiparesis but responding well to PT; in general very happy and energetic in appearance [12/10/10] 340 days post explant
007-105	30 d	Unable (28 d)	10 (38 post tx)	10 (38 post tx)	Severe > 2.0	12 month post explant, PSOM 4/6/11; severe delay [05/01/11] 386 days post explant
010-107	16 d	3 (16 d)	4.5 (pre)	N/A	N/A	Support withdrawn

# Trial Results: Neurological SAEs

PSOM at last follow-up post explant in patients with neurological dysfunction

Median time to PSOM assessment = 43.5 days post explant

Cohort	Normal	Mild/ Moderate	Severe/ Support withdrawn
Cohort 1	1	3	3
Cohort 2	1	3	3

Proportion with severe sequelae from neurological dysfunction: 12.5% (6/48)

# Trial Results: Neurological SAEs

Cohort	N	Patients with Event	# Total Events	Total time on support (Days)	Rate per Patient-Day [upper bound]
<b>1*</b>	<b>24</b>	<b>7</b>	<b>8</b>	<b>1411</b>	<b>0.006 [0.011]</b>
ECMO Matched**	48	5	6	313	0.019 [0.042]
<b>2*</b>	<b>24</b>	<b>7</b>	<b>9</b>	<b>1376</b>	<b>0.007 [0.012]</b>
ECMO Matched**	48	5	7	337	0.021 [0.043]

\*EXCOR events reported per INTERMACS Definition

\*\*ELSO includes: Brain Death, Seizure with EEG, CNS Infarction, CNS Hemorrhage

# Pump Change Information–Cohorts 1 & 2

- 25 of 48 patients (52%) had at least 1 pump change
- 10 of 25 patients had  $\geq 2$  pump changes
- 46 total pump changes (43 for suspected thrombus)
- 38 LVADs, 2 RVADs and 6 BVADs were replaced

Variable	Mean $\pm$ Std	Range
Number of replacements	1.0 $\pm$ 1.2	0 – 4
Number of replacements per days on device	0.02 $\pm$ 0.03	0 – 0.125
Time to first replacement (days)	24.9 $\pm$ 20.9	4 – 105

# Pump Changes and Neurologic Events

14 patients in cohorts 1 & 2 had neurologic events

8 of 14 had a total of 17 pump changes

8 Pump changes in 5 patients occurred *before* a neurologic event

- 1 Pump change same day as neuro event
- 1 Pump change 1 day before neuro event
- 3 Pump changes 2 days before neuro event
- 3 Pump changes remote ( > 7 days ) before neuro event

11 Pump changes in 5 patients occurred *after* a neurologic event

- 2 Pump changes 2 days after neuro event
- 1 Pump change 3 days after neuro event
- 8 Pump changes remote ( > 7 days ) after neuro event

# Trial Results: Transplant Eligible Days

Cohort	N	Days on Device		Days on Transplant List	
		Median	Range	Median	Range
1	24	27.5	0 - 174	27.5	0 - 174
2	24	42.5	3 - 192	42.5	3 - 151

- **Transplant eligible means the patient is actively listed for heart transplantation**
- **One patient was temporarily removed from the transplant list then relisted and later transplanted**

# Trial Results: Conclusion

## Study Cohorts

Cohort	N	Success Rate	SAE Rate per patient-day
1	24	21/24 (87.5%)	96/1411 = 0.068 [0.083]
2	24	22/24 (91.7%)	107/1376 = 0.078 [0.094]
<b>TOTAL</b>	<b>48</b>	<b>43/48 (89.6%)</b>	<b>203/2787 = 0.073 [0.084]</b>

**SAE Rate success criteria: <0.25 events/patient-day**

# Trial Results: Conclusion

## Study Cohorts, Supporting Cohorts, ECMO Control

Cohort	N	Success Rate	SAE Rate per patient-day
1	24	21/24 (87.5%)	96/1411 = 0.068 [0.083]
2	24	22/24 (91.7%)	107/1376 = 0.078 [0.094]
1 CAP Small BSA	20	16/17 (94.1%)	74/1330 = 0.056 [0.070]
Compassionate Use Small BSA	35	21/33 (63.3%)	135/1993 = 0.068 [0.080]
Compassionate Use Large BSA	6	5/6 (83.3%)	40/240 = 0.167 [0.227]
ECMO Control	96	63/96 (65.6%)	363/650 = 0.558 [0.619]

# Trial Results: Conclusion

## Neurological Dysfunction

Cohort	N	% with event	SAE Rate per patient-day [upper 95% conf bound]
1	24	29.2%	0.006 [0.011]
ECMO Matched	48	10.4%	0.019 [0.042]
2	24	29.2%	0.006 [0.012]
ECMO Matched	48	10.4%	0.021 [0.043]
ECMO Literature*	773	15.0%	0.01-0.02

\*Almond, *Circulation*. 2011; 123(25):2975-84

## ***EFFECTIVENESS OBJECTIVE:***

The primary objective of the study was to demonstrate that the survival rate in subjects treated with the EXCOR® Pediatric was different from the survival rate in the historical control of subjects treated with ECMO as a bridge to cardiac transplant.

## ***Hypotheses:***

$H_0$ : EXCOR® Survival = ECMO Survival

$H_A$ : EXCOR® Survival  $\neq$  ECMO Survival

***OBJECTIVE HAS BEEN MET***

## ***SAFETY OBJECTIVE :***

The primary objective of the study was to summarize the serious adverse event (SAE) rate calculated as the number of serious adverse events per patient-day of support on EXCOR® Pediatric.

## ***Hypotheses:***

$H_0$ : EXCOR® SAE Rate  $\geq 0.25$

$H_A$ : EXCOR® SAE Rate  $< 0.25$

***OBJECTIVE HAS BEEN MET***

**The trial demonstrates that the requirements of the HDE application have been met:**

**“Safety and Probable Benefit”**

