2016 PAC Panel Meeting
Berlin Heart, Inc.
EXCOR Pediatric Ventricular Assist Device

Medical Device Report (MDR) Review, Post Approval Study (PAS) Review and Literature Review

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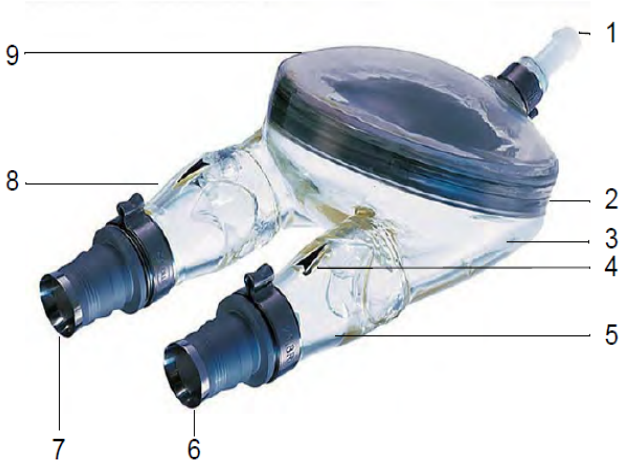
Indications For Use

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

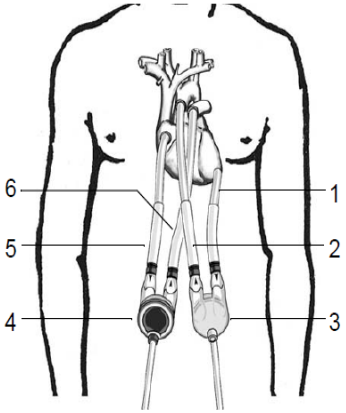
Berlin Heart EXCOR - Components

Extracorporeal, Pneumatically Driven Blood Pump



1 driving tube connector
2 triple-layer membrane
3 blood chamber (de-airir ple at back of pump)
4 arrow mark: indicates b flow direction
5 inflow stub
6 titanium connector: inflc – inflow cannula
7 titanium connector: outf stub – outflow cannula
8 outflow stub
9 air chamber

Biventricular Configuration



1 inflow cannula from LV apex
2 outflow cannula to ascending aorta
3 left pump (blood-chamber pointing upwards)
4 right pump (air-chamber pointing upwards)
5 inflow cannula from right atrium
6 outflow cannula to pulmonary artery

Inflow

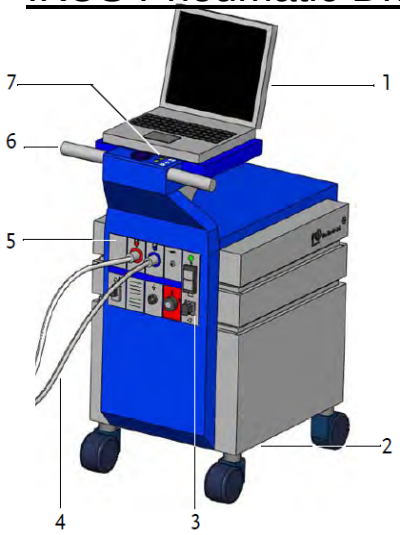
Atrial Cannula

LV Apex Cannula

Outflow

Arterial Cannula

IKUS Pneumatic Drive and Control Unit



1 laptop computer with monitor program
2 lifting bar
3 mains cable
4 driving tubes
5 connection panel
6 handle
7 display and operating panel

Medical Device Report (MDR) Review

Provided by:
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Medical Device Reports (MDR)

MDR Database Search Criteria

- Manufacturer Name: containing Berlin Heart
- Date Report Entered: June 1, 2015 – May 31, 2016

Search Results: 32 MDRs

Overview of 32 MDRs EXCOR VAD

Reporting Country

- US: 12 (37.5%)
- OUS: 20 (62.5%)

Patient Gender

- Male: 17 (53%)
- Female: 15 (47%)

Patient Age

- **Pediatric*: 31**
  - **Range: 1 month – 15 years; Mean: 3.4 years**
- Adult: 1
  - 34 year old

*Pediatric: Age <22

Event Type of 32 EXCOR MDRs

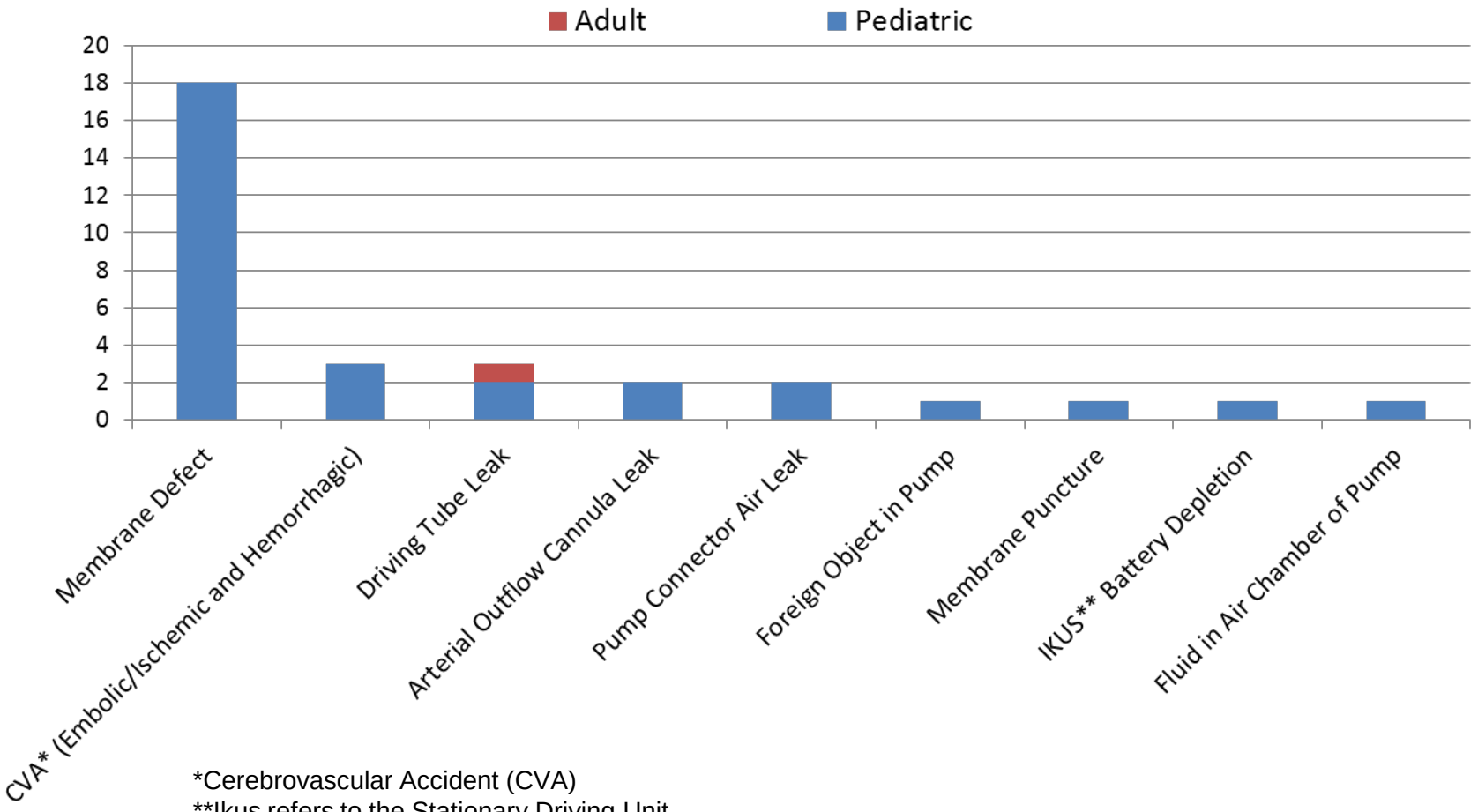
	Pediatric	Adult	Total
Death	0	0	0
Serious Injury*	6	0	6
Malfunction**	25	1	26
Total	**31**	**1**	**32**

*Serious Injury per regulation (CFR803.3) is defined as an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

**A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Berlin Heart EXCOR
Primary Reported Problems

(n=32)



*Cerebrovascular Accident (CVA)
**Ikus refers to the Stationary Driving Unit

Primary Reported Problems by Event Type

Reported Problem	MDR Count	Death	Injury[1]	Malfunction[2]	TTEO* (months)
Pre-Procedural	**1**	**0**	**0**	**1**	
Foreign Object in Pump	1	0	0	1	0
Post-Procedural	**31**	**0**	**6**	**25**	
Membrane Defect	18	0	3	15	1.0 - 8.9
CVA (Embolic/Ischemic and Hemorrhagic)	3	0	3	0	0.3 - 1.7
Driving Tube Leak	3	0	0	3	4.1 - 9.2
Arterial Outflow Cannula Leak	2	0	0	2	1.7 - 2.8
Pump Connector Air Leak	2	0	0	2	2.9 - 3.5
IKUS Battery Depletion	1	0	0	1	UNK
Fluid in Air Chamber of Pump	1	0	0	1	0.03
Membrane Puncture	1	0	0	1	0.03
Total MDRs	**32**	**0**	**6**	**26**	

[1] Serious Injury per regulatory definition (CFR803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

[2] A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

*TTEO is the time to Event Occurrence.

MDR Count for 2016 Reported Problems Compared to 2015 Analysis

Reported Problem	MDR Count 2016 Analysis (n=32)	MDR Count 2015 Analysis[1] (n=43)
Membrane Defect	18 (56%)	22 (51%)
CVA* (Embolic/Ischemic and Hemorrhagic)	3 (9%)	7 (16%)
Driving Tube Leak	3 (9%)	5 (12%)
Arterial Outflow Cannula Leak	2 (6%)	1 (2%)
Arterial Outflow Cannula Rupture	0	2 (5%)
Pump Connector Air Leak	2 (6%)	0
Foreign Object in Pump	1 (3%)	0
Membrane Puncture	1 (3%)	0
IKUS** Battery Depletion	1 (3%)	0
Fluid in Air Chamber of Pump	1 (3%)	0

[1] Note that this count is not an exhaustive list of reported problems from 2015

*Cerebrovascular Accident

**IKUS refers to the Stationary Driving Unit

Summary of MDR Review

- The injury and malfunction MDRs related to CVA, membrane defects, and driving tube leaks are similar to reported events from the previous year and in the IDE. The manufacturer has implemented manufacturing changes to address membrane defects and driving tube leaks.
- There were two malfunction events related to leaks of the outflow cannula. The IFU was updated in late 2015 to address post market experience, including labeling enhancements addressing the proper cannula care and relevant precautions for the cannulas including activity restrictions
- No other safety concerns at this time

Berlin Heart EXCOR Post-Approval Study Update and Literature Review

Provided by: Rebecca Ward, MPH
Epidemiologist

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Post Approval Study (PAS) Summary

PAS Phase I
Clinical results to primary outcome of interest (death, transplant, successful wean) (N=39)

Reported at 2015 PAC

- Survival Rate 70% (27/39)
- SAE Rate 0.02/pt. days of support*
- Total CVA 33% (13/39)
  - 8 deaths (5 CVA related)

Post Approval Study Landmarks:

- Enrollment concluded March 2014
- All patients reached Primary Outcome of Interest by February 2015 (Phase I)
- NEW: Functional and Quality of Life (QoL), Stroke Outcomes Updates received August 2016 (Phase II)

PAS Phase II
Continued follow-up to 24 months of patients surviving to transplant or successful wean (n=27)

- 1 death 8mo. Post Transplant
- 1 Re-implanted with BHE

Patients Eligible for Long Term (24 month) Functional, QoL and Stroke Outcomes Assessments (n=25)

Survivors completing 24 mo. follow-up by July 2016 (n=20)

- Functional Status II (FSII)
- Pediatrics' Quality of Life (PEDS QL)**
- Pediatric Evaluation of Disability Inventory (PEDI)**

All Stroke Survivors (n=5)

- Pediatric Stroke Outcomes Measure (PSOM)

*IDE rate = 0.07 SAE per pt. days of support, $p < 0.0001$

** Data included in Executive Summary

Functional Assessment (FSII)

Score	Baseline		12 month post explant		Change Baseline to 12 month post	
	N	Median [IQR]	n	Median [IQR]	n	Median [IQR]
Total Overall age groups	28	66.1 [51.8 , 78.6]	20	83.9 [71.4 , 89.3]	16	16.1 [3.6 , 25.0][2]
Total Within age group	28	68.6 [50.0 , 76.7]	20	79.5 [74.7 , 91.2]	16	15.0 [1.0 , 24.5][2]
General Health	28	65.0 [47.1 , 75.0]	20	76.5 [73.5 , 91.4]	16	12.5 [2.3 , 27.1][2]
Responsiveness/ Activity/ Interpersonal Functioning[1]	28	71.4 [60.4 , 76.0]	20	78.6 [71.4 , 85.0]	16	7.1 [0.0 , 14.1][2]

[1] Scale is called Responsiveness for age < 2 years, Activity for ages 2-4 years and Interpersonal Functioning for ages 4+ years
[2] Wilcoxon test significant p<0.05

FSII assesses general health and life-stage specific factors for the child over a two week period

- Children age 0 months to 11 years, grouped into age ranges
- Completed by caregiver
- Higher scores better

Total scores, general health scores, and responsiveness/activity/interpersonal functioning scores were significantly improved from baseline to 12 months post-explant/transplant

Pediatric Stroke Outcome Measure (PSOM)

- Deficits assessed in 5 domains
  - left sensorimotor abilities
  - right sensorimotor abilities
  - language production
  - language comprehension
  - cognition/behavior
- Each Domain Scored from 0 to 2:
  - 0 = no deficit
  - 0.5 = mild deficit
  - 1 = moderate deficit
  - 2 = severe deficit
- Total worst possible score (all domains) = 10
- Score Changes over time
- Total Score $\geq$ 2 = Severe Deficit

Stroke Outcome Assessment

PSOM for Subjects (n=5) that survived after Stroke

Outcome	Days of support	PSOM SCORES					Clinical Notes on Current Health Status
		Time of SAE	30 day Post SAE	60 day Post SAE	12 mo. post - explant	24 mo. post-explant	
Transplant	78	2	7.5	4	2	2	24 month post: Active 3 year old ambulating fully; has some gross motor delay/limitations which have improved and speech is close to normal age level
Transplant	208	1	2.5	1	0	1	24 month post: Well appearing but quite thin
Transplant	120	2	2.0	0	ND	Due July 2016	12 month post: Continues well clinically and has successfully weaned off diuretics; asymptomatic with stable ECHO, EKG and lab work
Transplant	160	ND	ND	ND	4	ND	24 month post: Appetite and activity level are good; taking steps by herself. Significant improvement in language development.
Weaned	40	Parents refused testing					24 month post: Needs help with most things and unable to ambulate

Summary of PAS update

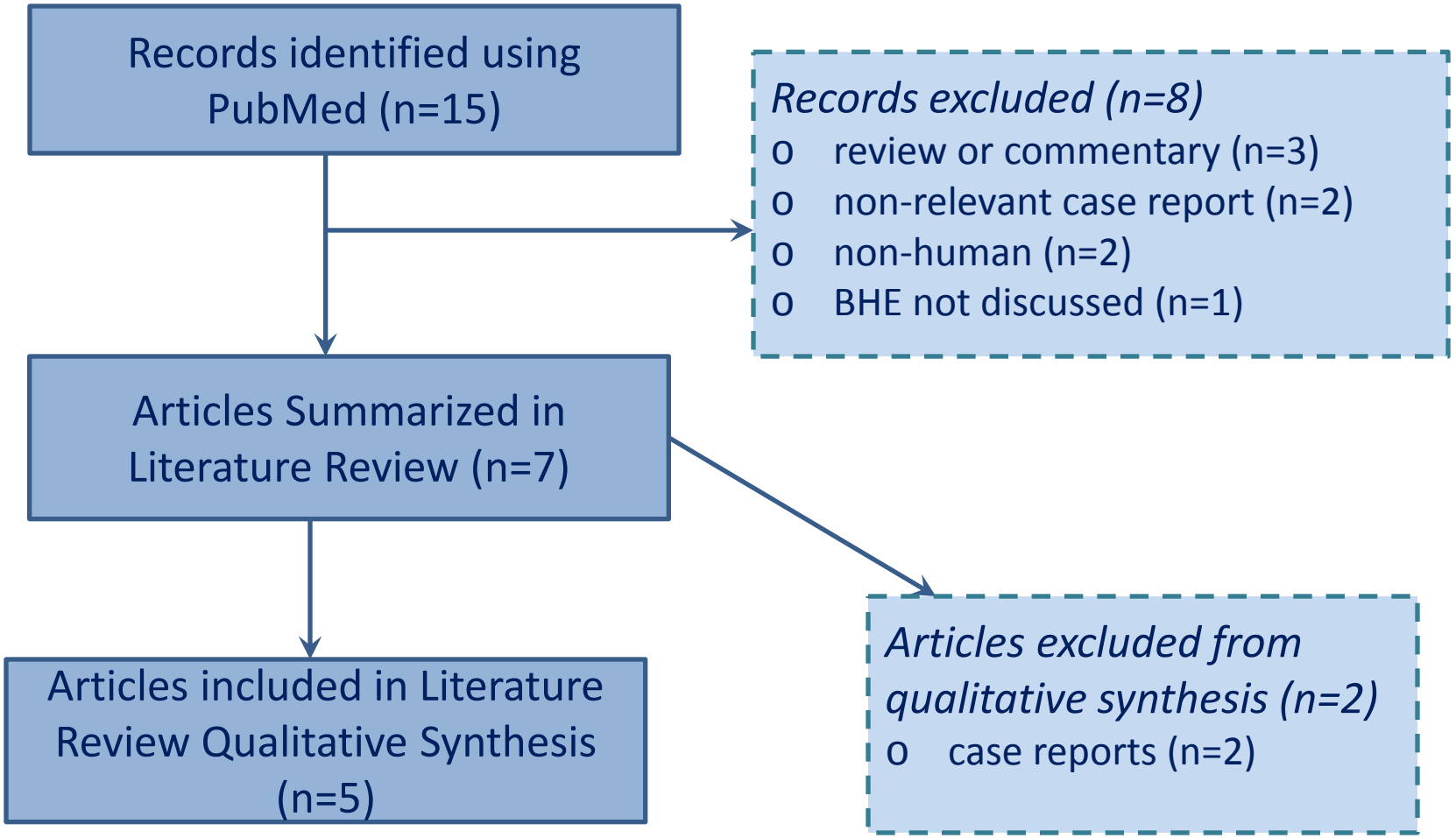
- Survival after transplant or successful weaning is high
- Subjects that survived to transplant after a stroke are reportedly improving or doing well
- Limited data are available regarding the longer-term quality of life and functional outcomes for study subjects. The assessment with the most complete data shows statistically significant improvement in functional outcomes from baseline to 12 months post-transplant or explant.
- No additional concerns raised from longer-term follow-up of subjects from this PAS

Literature Review

Purpose of Literature Review: To evaluate probable benefits and risks associated with the device

Searched PubMed for articles published since last year's search (06/01/2015 – 05/31/2016) using the same terms and limits as previous years

Literature Review



Qualitative Synthesis Literature Review Update (n=5)

5 retrospective cohort studies

- 1 North America, 1 Australia, and 3 Europe
- 1 of 5 studies included pediatric and young adult populations (Shi et al. 2015)
  - Mean age 15 years; Range 14 days to 25 years
- 4 of 5 studies pediatric only populations (<22 years of age)
  - Median age 23.8 months – 9.1 years; Range 3 days to 17.9 years old
- Patients Implanted with BHE
  - As early as 1990 and as late as 2014

3. De Rita, F., et al., *Outcome of mechanical cardiac support in children using more than one modality as a bridge to heart transplantation.* Eur J Cardiothorac Surg, 2015. **48**(6): p. 917-22; discussion 922.

4. Shi, W.Y., et al., *Outcomes of ventricular assist device implantation in children and young adults: the Melbourne experience.* ANZ J Surg, 2015.

5. Hetzer, R., F. Kaufmann, and E.M. Delmo Walter, *Paediatric mechanical circulatory support with Berlin Heart EXCOR: development and outcome of a 23-year experience.* Eur J Cardiothorac Surg, 2016.

6. Niebler, R.A., et al., *Ventricular Assist Device in Single-Ventricle Heart Disease and a Superior Cavopulmonary Anastomosis.* Artif Organs, 2016. **40**(2): p. 180-4.

7. Sandica, E., et al., *Long-Term Mechanical Circulatory Support in Pediatric Patients.* Artif Organs, 2016. **40**(3): p. 225-32.

Pediatrics: Probable Benefit

- Survival on BHE
  - Reported in 3 studies (Hetzer et al. 2016; Niebler et al. 2016; Sandica et al. 2016)
  - Ranged from 65% (Hetzer et al. 2016) to 90% (Sandica et al. 2016)
- Survival from BHE support to transplant
  - Reported in 4 studies (DeRita et al. 2015; Hetzer et al. 2016; Niebler et al. 2016; Sandica et al. 2016)
  - Ranged from 61% (Hetzer et al. 2016) to 81% (DeRita et al. 2015)
- Survival for subjects with potentially higher risk
  - Reported in 2 studies
  - Single ventricle vs. dual ventricle physiologies (Niebler et al. 2016)
  - Patients needing single vs. multiple modalities of Mechanical Circulatory Support (DeRita et al. 2015)

Pediatrics: Safety

- Neurologic adverse events while on BHE
  - Composite Neuro AE (available from two studies)
    - 10.3% (Sandica et al. 2016) and 41.2% (Niebler et al. 2016)
  - Hemorrhagic CVA (reported in two studies)
    - 3.4% (Sandica et al. 2016) and 47% (Hetzer et al. 2016)
  - Thromboembolic Events (reported in two studies)
    - 6.9% (Sandica et al. 2016) and 22% (Hetzer et al. 2016)
- Device-related Infection
  - Reported in two studies
  - 3.4% (Sandica et al. 2016) and 67% (Hetzer et al. 2016)

Literature Review Summary

- Berlin Heart EXCOR continued to be associated with a relatively high rate of survival while on the device and survival to transplant

- Use of the device was associated with neurologic adverse events, and infection

- Adverse events observed in this year's literature search are similar across what was observed in last year's literature search, the IDE study, and the PAS

FDA Summary

- FDA's Review Team has identified no new safety concerns since September 2015's PAC meeting
- FDA concludes that the probable benefit/risk profile of the device for the pediatric population continues to support the HDE for which the exemption was granted

FDA Recommendation

Continue surveillance and report updates of the following to the PAC in 2017:

- MDR Review
- Mandated Post-Approval Study Review
- Literature Review

Question to the PAC

Does the Committee agree with CDRH's conclusions and recommendations?