FDA Executive Summary

Prepared for the **September 14, 2016** meeting of the FDA's Pediatric Advisory Committee

H100004

Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device

Introduction

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-marketing experience with the use of the Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device (PVAD) in pediatric patients since approval. The EXCOR PVAD is an extracorporeal pneumatically pulsatile ventricular assist device intended as a bridge-to-cardiac transplant (BTT) or to provide circulatory support for cardiac transplant candidates in the pediatric population. It was approved as a Humanitarian Use Device (HUD) in December 2011 by the Center for Devices and Radiological Health under Humanitarian Device Exemption (HDE) application H100004.

The purpose of this review is to provide the Pediatric Advisory Committee with post-marketing safety data so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This memorandum will include summaries of the post-market medical device reporting (MDR) for adverse events, post-approval studies, and the peer-reviewed literature associated with the device. At the panel meeting, the Agency will ask for your input on whether the benefit/risk profile of the device for the pediatric population continues to support and confirm the information provided in the HDE application which led to marketing approval of the Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device (PVAD) as an HUD.

Indications for Use

EXCOR® Pediatric Ventricular Assist Device (referred to as EXCOR) 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.

Contraindications

Patients unable to tolerate systemic anticoagulation therapy should not be implanted. Magnetic Resonance Imaging (MRI) is contraindicated in patients after being implanted with the EXCOR.

Device Description
The EXCOR® consists of one or two extracorporeal pneumatically driven blood pumps (depending on univentricular or biventricular support), cannulae to connect the blood pumps to the atrium or ventricle and to the great arteries, respectively, and the IKUS driving unit.

DEVICE DISTRIBUTION DATA

FDASIA amended section 520(m) of the FD&C Act to allow devices with HDEs indicated for use in pediatric patients or a pediatric subpopulation to be sold for profit; the number of devices distributed in any calendar year cannot exceed the Annual Distribution Number (ADN) for each device. The ADN is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States. The FDA has interpreted this to mean that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual.

For Berlin Heart, one device is reasonably necessary to treat an individual; therefore the ADN for this device is 4,000. A total of 1754 devices have been shipped to North American sites since initial marketing approval (December 16, 2011). From November 30, 2014 to November 30, 2015, a total of 279 devices were shipped to US sites. In addition to the Post Approval Study (PAS, n=39), a total of 208 patients have been implanted with the EXCOR® Pediatric device at 42 hospitals from the time of HDE Approval through March 31, 2015. There were sixty US implants in 2015. The PAS, which is now closed, enrolled patients from July 27, 2012 to March 10, 2014. All but a small percentage of the devices implanted since HDE approval have been in pediatric (<22 years) patients.

OVERVIEW OF MDRS

Strengths and Limitations of MDR Data
Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/environment, including:
    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subject to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with Berlin Heart EXCOR Pediatric Ventricular Assist Device

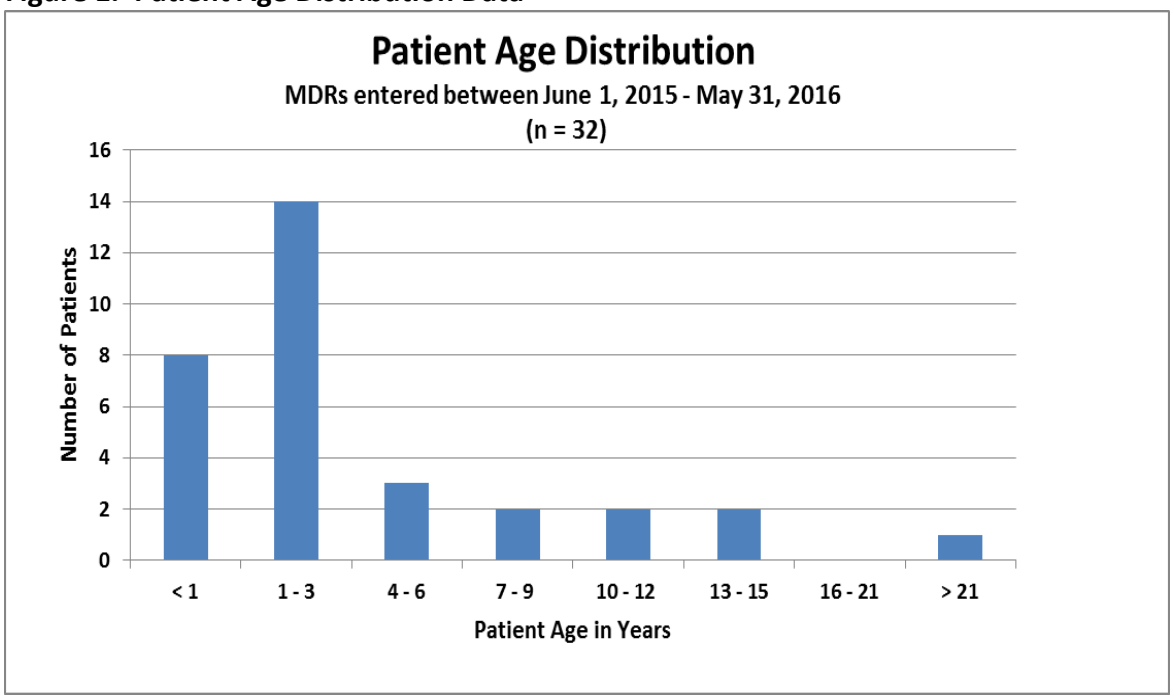
The Agency received 32 MDRs related to the Berlin Heart (BH) EXCOR pediatric ventricular assist device which were entered into FDA's MDR database between June 1, 2015 and May 31, 2016. The MDRs were reviewed for factors such as reported device and patient problems, event type, report source, patient age, patient sex, reporting country and the time to event occurrence (TTEO). The TTEO is based on the implant duration specified in the event text of the MDR or calculated as the time period between the date of implant and date of event. These factors are characterized in the results summary.

Results

Of the 32 MDRs, there were 31 MDRs reported by the manufacturer and 1 MDR reported from a user facility (UF).

Patient age data was provided in all 32 MDRs. There were 31 pediatric patients ranging in age from 1 month to 15 years of age with an average age of 3.4 years. There was 1 adult male patient who was 34 years old. Patient gender information was provided in all 32 MDRs of which 17 were male and 15 were female. See Figure 1 for the age distribution data.

Figure 1. Patient Age Distribution Data

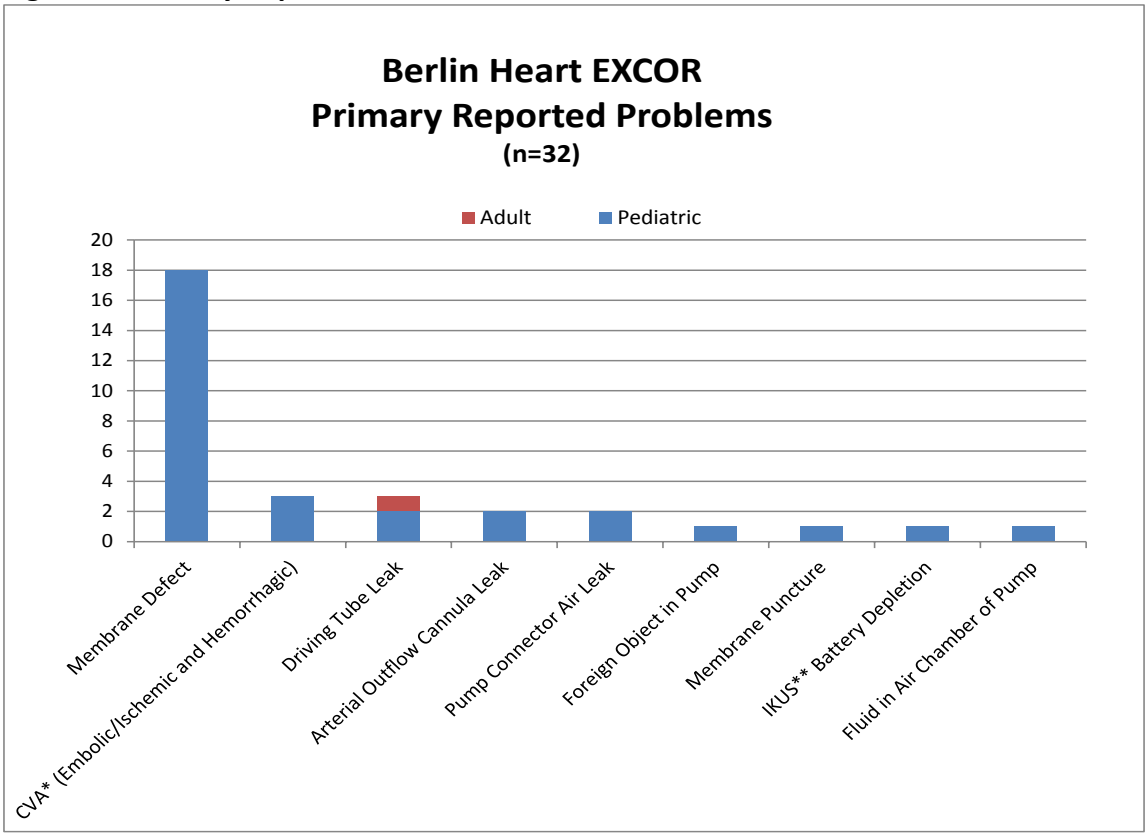


The Reporting Country was available in all 32 MDRs and included the United States (US) for 12 MDRs and Out-of-US (OUS) for 20 MDRs. OUS countries included Poland (6 MDRs), Germany (3 MDRs), Canada (2 MDRs), United Kingdom (2 MDRs), Australia (1 MDR), Chile (1 MDR), France (1 MDR), Italy (1 MDR), Japan (1 MDR), Sweden (1 MDR) and Switzerland (1 MDR).

Reported Problems

The 32 MDRs were individually reviewed and analyzed for the primary reported problem. Figure 2 depicts the number of MDRs categorized by the primary reported problem.

Figure 2. Primary Reported Problems in the 32 MDRs



* Cerebrovascular Accident
** IKUS refers to the Stationary Driving Unit

Among the 32 MDRs, the most commonly reported problem was "Membrane Defect" in 18 MDRs (56%). The next most commonly reported problems were embolic/ischemic or hemorrhagic cerebrovascular accident (CVA) in 3 MDRs (9%) and "Driving Tube Leaks" in 3 MDRs (9%). These and the other reported problems are described in further detail in the Type of Event section following Table 2.

The number of MDRs for each reported problem in this year's analysis was also compared with the number of MDRs reported for these problems in the 2015 analysis in Table 1 below. Note that this table is not an exhaustive list and does not include all reported problems from last year's analysis. However, the arterial outflow cannula rupture death events from the 2015 analysis are included to provide a comparison to the events in the 2016 analysis.

Table 1. MDR Count for 2016 Reported Problems compared to 2015 Analysis

Reported Problem	MDR Count 2016 Analysis (n=32)	MDR Count 2015 Analysis (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

*Cerebrovascular Accident
**IKUS refers to the Stationary Driving Unit

Type of Events

The type of events in the 32 MDRs were categorized as 2 injuries, 28 malfunctions and 1 "blank" where the type of event was not reported. The MDRs were individually reviewed and based on the information, 3 malfunctions and 1 "blank" MDR were determined to be injury reports, resulting in an adjusted total of 6 injuries and 26 malfunctions. There were no deaths reported in the MDRs. Table 2 lists the total MDR count for each primary reported problem along with the type of event and TTEO. Following the table, the primary reported problems are further detailed to include specific event, patient information, TTEO and required intervention.

Table 2. Reported Problems by Type of Event and TTEO in the 32 MDRs

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 the event occurrence.

Pre-Procedural event (n = 1)
There was one pre-procedural malfunction event reported by a UF which occurred during preparation of the device for implantation.

- **Foreign Object in Pump (n=1)**
  A UF reported that plastic was discovered in the blood pump during priming. The manufacturer's analysis indicated that a small piece of material was shaved off of the de-airing port when the trocar needle was turned during insertion causing it to protrude into the pump chamber. This was a user issue and a new pump was primed and used on the patient. The Instructions for Use (IFU) instructs the user not to turn the trocar as it increases the risk of removing a piece of silicone material in the de-airing nipple.

Post-Procedural Events (n=31)
There were 31 MDRs related to post-procedural events. There were 6 injury reports and 25 malfunctions. Further information on the reported problem and event details are described below:

- **Membrane Defects (n=18)**
  There were three (3) injury and 15 malfunction MDRs related to membrane defects to either the blood or air membrane of the pump or to the stabilization ring. The issues are described as failure of the pump to fill or eject properly, reduced cardiac output, air padding between membrane layers, and blood in front of or in the area around the

stabilization ring in the blood side layer or air side layer of the triple layer membrane. These events are consistent with issues reported in previous years. The three (3) injuries and 13 of the 15 malfunctions were reported from OUS countries. MDRs include patient age ranges between 9 months to 15 years. The TTEO ranges for these events were from 1 to 8.9 months with an average of 4.3 months.

The 3 OUS injury reports are further described below:

- A one year old female with left ventricular assist device (LVAD) configuration on the pump for 68 days experienced a decrease in cardiac output. A membrane defect of the blood pump was suspected and the patient required sedation and intubation for pump exchange. The pump was exchanged and the patient was doing well.
- A nine month old male with biventricular (bi-VAD) configuration experienced increased heart failure and was transferred to the ICU. The left side pump appeared to be in intermittent contact with the inner wall of the outer shell after 205 days in use. The pump was exchanged and the patient tolerated the exchange well.
- A four year old male supported in a bi-VAD configuration for 119 days was noted to have unstable hemodynamics. The IKUS was changed which did not result in improvement. The right pump was exchanged during which the patient had a low cardiac output. After the pump exchange, the patient's hemodynamics stabilized. The pump was not returned by the UF. Due to the general poor health status of the patient, it was decided to withdraw support.

According to the manufacturer analysis provided in the MDRs reporting membrane defects, "the blood pump is designed with a triple layer membrane separating the air chamber from blood chamber for safety reasons. The entire membrane consists of an air-side layer, a middle layer and a blood-side layer. In case of disruption in one of the triple layers, there are two more layers that will maintain the integrity of the air and blood chambers". The IFU warns the user to visually check pump function every four (4) hours including filling and ejecting over several pump cycles, and to change the pump if a problem is detected.

In 11 of the 18 MDRs, the manufacturer analysis includes remarks about graphite coating/particles in the membrane interstices which may have been caused by the abrasion of the membranes over time. These graphite particles between the membrane layers most likely caused increased friction at certain points which finally led to the defect and/or hole in the air membrane and middle layer of the membranes. When this defect occurs, air can get between the membrane layers and form an air cushion.

The remaining malfunction MDRs include problems with the reduced membrane thickness from an uneven load on the membrane caused by membrane layers not being exactly parallel to each other and a hole in the air side membrane from crystallized sodium chloride particles inadvertently entering the air chamber during priming.

The manufacturer incrementally implemented a number of changes in the production process between 2013 and 2015 to mitigate membrane layer defects. There was one of the eighteen MDRs in which the pump was produced after all of the design and manufacturing enhancements were incorporated. The FDA will continue to monitor for defects in devices produced after all of the incorporated changes.

- **CVA (Embolic/Ischemic and Hemorrhagic) (n=3)**
  There were three (3) injury events where CVAs were reported. There was one patient who had an embolic/ischemic CVA, one patient with a hemorrhagic CVA and one patient who had both an ischemic and hemorrhagic CVA. The three (3) events occurred in the US.
    - A mobile thrombus was identified in the pump nine (9) days after LVAD implant in a 16 month old male. On the way to the operating room (OR) to exchange the pump, the patient experienced right-sided weakness. The pump was exchanged and a computed tomography (CT) scan performed after the exchange revealed a large MCA thrombolytic infarct. An echocardiogram identified a thrombus in the apex, impeding flow through the apical cannula. The patient was removed from LVAD support the next day, tolerated the procedure well, and was recovering from the event.
    - A male patient just under one year of age was supported with an LVAD for 52 days when decreased movement of his left side was noted. A CT scan revealed a hemorrhagic CVA. The patient had previously experienced persistent deposits in the pump and the unfractionated heparin levels were being maintained at 0.8-0.9 while on a heparin drip as a result. The patient was sent to the OR for an external ventricular drain. The patient tolerated the procedure well and the pump was filling and ejecting normally. The patient remains intubated and is moving around.
    - A one month old male was supported for 32 days in an LVAD configuration when he had changes in pupil movement and stopped tolerating feeds. A head CT revealed bilateral multifocal ischemic infarcts with loss of gray/white matter differentiation and hemorrhagic infarct in the frontal lobe. The age of the infarcts was indeterminate. The family withdrew support and the patient expired the same day.

- **Driving Tube Leak (n=3)**
  There were three (3) malfunction events involving air leaks or a crack in the driving tube/drive line of the device and is consistent with MDRs reported in past years. The leaks/cracks were identified as occurring at the point of connection to the blood pump or at the passage from the thinner to thicker diameter tube close to the blood pump. This area of the driving tube is where the most stress is applied by external forces during use occurring in more active patients. These events involved patients ranging in age from 6 years to 34 years of age with a TTEO between 4.1 to 9.2 months. A design change was approved in September 2014 with an added strain relief which blends in

with the tube and provides more protection from stress fatigue. The driving tubes in the three events were manufactured prior to the design changes.

- **Arterial Outflow Cannula Leak (n=2)**
  There were two (2) malfunction events that occurred on one (1) US male patient one (1) year of age on days 52 and 84. The patient's nurse noticed a drop of blood on the outside of the connecting tubing set connected to the outflow side of the pump near the titanium connector. The blood leak was reproduced by bending the cannula away from the site of the blood. The EXCOR pump was exchanged and the compromised tubing was trimmed off. The second event occurred approximately one (1) month later when the pump was exchanged due to a leak in the connecting set tubing connected to the outflow side of the pump. The evening of the event, a nurse noted blood on the outside of the pump and connector as well as in the patient's mouth. The patient had been witnessed chewing on the cannula and connector in the past. The pump and connecting set were exchanged and there was no harm to the patient in either event. Manufacturer investigation of the first event including microscopic analysis identified a small cut or incision on the outer surface of the tubing. The inner tubing looked more rupture-like, allowing the drop of blood to leak through. There were imprints of the cable tie detected on the outside of the tubing partially overlapping the visible incision and damage. Based on the appearance of the damage, it was determined the tubing was cut externally creating an incision which developed into a tear in the interior of the tubing until the tubing ruptured. A drop of blood was noted on the outer surface of the connector set. In the second event, the UF discarded the pump and connecting set. According to information provided by the site, the tube may have leaked due to the patient chewing the tubing. The IFU was updated in late 2015 to reinforce proper care and precautions for cannulas based on the two (2) arterial outflow cannula rupture events and one (1) arterial outflow cannula leak from last year's analysis.

- **Pump Connector Air Leak (n=2)**
  There were two (2) malfunction events that occurred on one (1) OUS patient on days 87 and 105. The one (1) month old female patient was in a bi-VAD configuration. A small amount of air leakage was identified at the connector for the driving tube on the left pump. A driveline connector, or barb connector, is assembled into the pump through the polyurethane (PU) air chamber tube stub on the pump housing and secured with a 1-ear clamp under which a sliding ring is positioned. The issue was detected only when the driveline was slightly kinked. The pump continued to function properly, but was exchanged without harm to the patient. Approximately 3 months later, a small amount of air leakage was noted at the connector for the driving tube of the left pump. The pump functioned as intended but the clinic exchanged the pump and the patient is doing well. Manufacturer analysis of both events identified that the sliding ring of the 1-ear clamp created an indentation on the PU air chamber stub creating a small air channel inside the stub allowing a minimal amount of air to escape at the connector. The indentation of the sliding ring was likely formed when assembling the 1-ear-clamp

during manufacturing. The manufacturer identified that these are isolated incidents from one UF. FDA is following-up with the firm on this device issue.

- **IKUS Battery Depletion (n=1)**
  There was one (1) malfunction event where the IKUS Stationary Driving Unit alarmed "batteries discharged -use power supply" while the device had been on power supply for 10 – 20 minutes. The IKUS was functioning well at that time. The UF contacted the BH hotline and the service engineer reviewed the log files sent by the site. It was determined that the IKUS was being used on battery mode multiple times without allowing the batteries to fully charge. The BH service engineer communicated to the site to fully recharge the batteries. It was also reported that a long power cord and extension cord were being used by the UF to limit battery depletion. The next day, the site called the BH hotline to report that the IKUS alarmed, stopped pumping and the EXCOR stopped ejecting. The nurse used the manual hand pump to support the patient until the IKUS was exchanged. There was no consequence to the patient. Investigation by the firm and the log files determined the IKUS alarmed "batteries discharged-use power supply" more than 20 times before the IKUS stopped functioning. The right battery failed due to using the IKUS in battery mode without allowing enough time for batteries to fully recharge. The UF also utilized power cords other than what was provided by BH which were notably longer. The details for properly recharging the IKUS and using only BH components with the IKUS are clearly stated in the IFU.

- **Fluid in Air Chamber of Pump (n=1)**
  There was one (1) malfunction event during the EXCOR implant procedure, once the pump was connected to the patient and pumping, when blood was noticed in the air chamber of the blood pump. The BH clinical hotline was called and the clinician was advised to exchange the pump. The pump was exchanged and there was no impact to the patient. The manufacturer investigation identified that for blood to penetrate the blood chamber to the air chamber, all three layers must leak and blood has to pass through the membrane interstices. However, there was no blood residue detected in the membrane interstices. There was no defect to the blood pump and fluid likely entered the air chamber inadvertently through the driveline port during the procedure.

- **Membrane Puncture (n=1)**
  There was one (1) malfunction event where a three (3) month old male had just undergone a pump exchange for suspected thrombosis. Once the new pump was in use, blood was noted around the blood chamber membrane. BH clinical affairs recommended changing the pump. The pump was exchanged and there was no harm to the patient. Evaluation of the returned pump identified damage on the blood membrane layer opposite the de-airing port. The appearance and position of the membrane damage indicates the damage was caused by the de-airing needle during priming of the pump.

Conclusions

- The injury and malfunction MDRs related to CVA, arterial outflow cannula leaks, membrane defects, and driving tube leaks are similar to reported events from the previous year.
- There were two outflow cannula malfunction events in a single patient related to leaks caused by previously unanticipated patient-cannula interactions (chewing). The IFU was updated in late 2015 to address post market experience including labeling enhancements addressing the proper care and relevant precautions for the cannulas to mitigate previously identified risks of vigorous patient activity on cannula integrity. No recurrences of the events addressed by these labeling updates were observed in the current reporting period.
- A driving tube design change was approved in September 2014 and membrane defect manufacturing improvements were initiated in 2013 through 2015. There was one MDR related to a membrane defect that was produced after all of the design and production changes were incorporated. FDA will continue to monitor MDRs to evaluate the effectiveness of the design and manufacturing improvements.
- The risks/complications reported in the MDRs have been reported in the Investigational Device Exemption (IDE) study, have been identified in the IFU and reflect known complications of mechanical circulatory assist devices.

POST MARKET DATA

Non-Study Information (Berlin Heart 2015 Annual Report)

A total of 208 patients have been implanted with the EXCOR Pediatric device at 42 hospitals outside the post approval study through March 31, 2015. The first 46 patients were implanted following HDE approval (December 16, 2011) and before Berlin Heart Inc. received FDA approval for the Post Approval Study (PAS) protocol (July 27, 2012). The most recent 67 patients were implanted following the closure of the PAS to enrollment (March 10, 2014). The dates are as follows (PAS enrolled 39 patients from 7/27/12 through 3/10/14).
HDE Approved December 16, 2011
Last patient enrolled out of the 208 was 3/31/2015.

Outside PAS

Pt. Number	Timing of Implant	Date range of Implant
1-46	Pre PAS Approval (n=46)	12/16/11 to 7/26/12
47-140	Parallel with PAS enrollment (n=94)	7/27/12 to 3/10/14
141-208	Post PAS enrollment Closure (n=68)	3/11/14 to 3/31/15

Not all patients consented to be enrolled in the PAS. The PAS was also limited to 26 sites, 19 of which enrolled patients. Outside PAS implants came from 42 total sites. They are almost exclusively PEDS patients – One patient of the 208 was 22 years old and all the rest were < 18. All PAS patients were pediatric.

Data from the Sponsor was provided in the Table below*

Outcome	N (% of 208)
Transplant	147 (70.7%)
Weaned successfully	6 (2.9%)
Death	31 (14.9%)
Escalated therapy	11 (5.3%)
On device support	13 (6.3%)

*Information source: internal device accountability system and verbal reported information the implant details and outcomes

Post Approval Study H100004

Summary of On-Device Follow-Up

There is an ongoing Post Approval Study (PAS) for the Berlin Heart EXCOR Pediatric Ventricular Assist Device (H100004). The primary safety objective/endpoint of this PAS was to demonstrate that the serious adverse event (SAE) rate was no greater in this postmarket study than the SAE rate from the Investigational Device Exemption (IDE) study. The primary effectiveness objective/endpoint of this study was to evaluate the number of study subjects that died, had left ventricular recovery, or received a heart transplant. Secondary objectives were to summarize device malfunctions, evaluations of explanted pumps that were suspected of thrombus, and an assessment of the learning curve for physicians who implant the device. Subjects in this study were followed until they reached a primary outcome (described below) and then for an additional 24 months post-explant. As of last year's post approval study report, which was reviewed and summarized for the Pediatric Advisory Committee (PAC) meeting in 2015, all pediatric PAS subjects (n=39) had experienced one of the outcomes of interest: heart transplant, death, switching to a different method of mechanical circulatory support, or successful weaning from the device. It was noted in the last executive summary that the primary safety endpoint was met and that the SAEs rate per subject-day was significantly lower in the PAS compared to the IDE study (PAS SAE rate: 0.02 events per subject-day vs. IDE SAE rate: 0.07 events per subject-day, p-value < 0.0001). Major bleeding, neurological dysfunctions, and major infections were noted as the most common adverse events, which was similar to the IDE study results. Close to 70% of the PAS subjects survived to successful weaning or heart transplant, this was also noted as similar to the IDE study.

Continued Follow-Up

Follow-up of surviving patients is continuing for two years post-transplant or successful weaning. The current yearly report from the sponsor has been received. Updates on the survival of study subjects, summary tables of the completed 12 and 24 month functional, quality of life, and outcome assessments, and brief clinical summaries of the health status of study subjects who had experienced a stroke while on the Berlin Heart EXCOR device were provided.

As reported last year, of the 39 original study subjects, 27 were successfully transplanted or weaned. One of the surviving subjects has since needed to be re-implanted with a new Berlin Heart EXCOR device and was exited from the study. Another one of the 27 surviving subjects died eight months post-transplant. Therefore, 25 subjects have or are currently contributing to continued follow-up, and 20 of those subjects have completed their 24-month post-explant or post-transplant follow-up.

Assessment of Continuing Neurological Dysfunction

The Pediatric Stroke Outcome Measures (PSOM) is used to assess outcomes after strokes in pediatric patients. Specifically, PSOM scores deficits for five specific areas: left side sensorimotor abilities, right side sensorimotor abilities, language production, language comprehension, and cognition or behavior. Each of these five subsets can be scored from zero to two with zero indicating no deficit, and a score of two indicating severe deficit. A total maximum, or worst possible score, across all five subsets is a score of ten. According to the study design, PSOM scores were to be collected at the time of the neurological serious adverse event (SAE), 30-days post-SAE, 60-days post-SAE, and 12 and 24 months post-explant or transplant. Neurological SAEs during the on-device study period were observed in 13 subjects for a total of 17 neurological dysfunction events. Five of the 13 subjects survived to transplant or successful weaning. Four of these five surviving subjects provided at least one PSOM score, and three of the surviving subjects provided multiple Pediatric Stroke Outcome Measure (PSOM) scores for the study. The current health status of the five subjects and their reported PSOM scores were sent to FDA by the sponsor and are provided as Appendix 1 to this summary. According to the information provided in the brief clinical summaries, four of five of the subjects were noted as either doing well or showing improvement in the continued follow-up period.

Functional Assessments

Two functional assessments were completed during the on-device study period and the continued follow-up: the Pediatric Evaluation of Disability Inventory (PEDI), and the Functional Status II (FSII). Summary tables of data from these assessments were sent to FDA by the sponsor and are provided as Appendix 2 to this summary.

PEDI is a clinical assessment of the functional and performance capabilities of children between the ages of six months and 7 years. In the patient assessment, children score 0 points if they cannot complete the skill mentioned in the assessment and 1 point if they can. Therefore, a higher score should be indicative of better functional ability. The caregiver assessment scores rank the child's need for assistance with functional tasks, 0 indicating the need for total assistance from the caregiver and 5 indicating the ability of the child to perform the task independently. Again, a higher score is better. Not all eligible subjects or caregivers of the subjects completed the inventory. Less than half of the subjects followed post-explant or transplant have contributed a PEDI assessment. Of the subjects that completed a baseline (completed 48-hours prior to device implant) PEDI assessment and a PEDI assessment post-

explant or transplant. While no statistically significant differences in scores from baseline to post-explant or transplant were reported, it should be noted that making conclusions about the difference in scores from baseline to continued follow-up assessments is difficult given the small number of completed assessments

FSII is used to assess general health and life-stage specific factors for a child over a two-week period. Children ages zero months to 11 years can be evaluated. The FSII questionnaire is completed by the primary caretaker, and scoring is calculated as a percentage of the maximum number of points possible for a specific age range. Higher scores are better. This assessment was completed by the majority of eligible study subjects at baseline, and the majority of eligible subjects at 12-months post-explant or transplant. Statistically significant improvement in total scores (overall and within age group), general health scores, and responsiveness/activity/interpersonal functioning scores were reported from baseline to 12-months post-explant or transplant.

Quality of Life Assessment

The Pediatrics Quality of Life assessment (PedsQL) uses assessments of psychosocial health and physical health to score the quality of life of pediatric patients. The PedsQL is completed by the primary caretaker for children age 2 years and older, and it can also be administered directly to the child if the child is age five or older. Higher scores are associated with a better quality of life. The majority of primary caretakers completed this assessment at baseline and approximately one-fifth of eligible children completed this assessment at baseline. Of the caretakers that completed a baseline assessment approximately half completed a post-explant or transplant PedsQL assessment, and of the children that completed a baseline assessment approximately one-third completed a post-explant or transplant assessment. Statistically significant improvements in total and psychosocial health scores were reported when caretakers completed an assessment for their child at baseline and 12 months post-explant or transplant. A summary table of these results was provided by the sponsor and is included as Appendix 3 to this summary.

PAS Conclusions

Survival after transplant or successful weaning is high. The majority of subjects that survived to transplant or successful weaning, after experiencing a neurological SAE while on BHE support, appear to be improving or doing well based on brief clinical assessments received from the sponsor. However, it should be noted that the information provided on the health status of these subjects was limited. Differences in functional assessment and quality of life scores from baseline to 12-months post-explant or transplant have not been statistically different or have shown statistically significant improvement. No statistically significant declines in quality of life or functional assessments were observed from baseline to continued follow-up. Again, it should be emphasized that there are limited data available regarding longer-term quality of life and functional outcomes for study subjects. Limitations of the quality of life data and functional assessments included high percentages of missing data, and a lack of consistency in the

completion of the different assessments. Conclusions regarding the lack of statistical significance for the change in scores from baseline to continued follow-up may be attributable to a lack of statistical power to detect differences. No additional concerns have been raised from the longer-term follow-up of the subjects from this PAS.

LITERATURE REVIEW

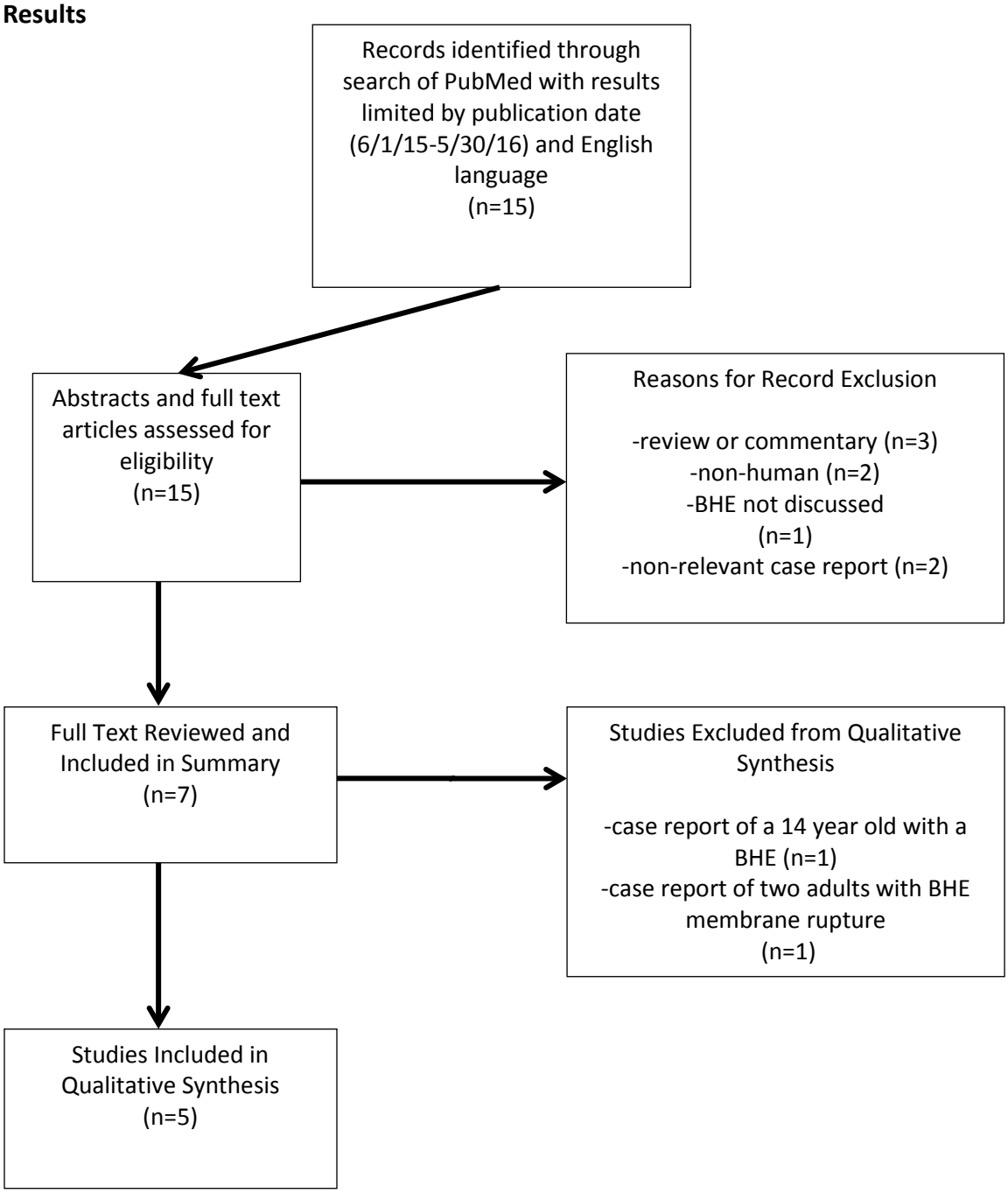
Methods

A literature review was conducted to update the PAC on any newly available literature since the last meeting on September 16, 2015. Specifically, this literature review was performed to detail the following based on the newly available literature:

1. The probable benefit of the Berlin Heart EXCOR VAD including the following endpoints: successful transplantation, successful weaning from device, and overall survival.
2. The adverse events associated with the Berlin Heart EXCOR VAD during and after use of the device.

On June 6, 2016, a search of the PubMed database for articles published since the prior literature review (June 2015) was conducted. The search terms used were the same as previous years' and were: "Berlin Heart" OR "Berlin EXCOR" OR "HEART EXCOR" OR EXCOR. Articles were excluded if they were not in English, if Berlin Heart use in humans was not discussed, and if the article was a review or commentary. Case reports were reviewed and summarized, but were not included in the qualitative analysis. The search was further limited to publications between June 1, 2015 and May 31, 2016.

Results



Through the PubMed search, 15 potentially relevant new articles were identified. Eight articles were determined to be irrelevant to this literature search after abstract and full text review. Three of the excluded articles provided a review or commentary. Two were excluded because they were not studies of humans. One was excluded because other ventricular assist devices were discussed, but the safety or effectiveness of the Berlin Heart was not. Four case reports were reviewed, of which two were excluded from summary due to lack of relevance.

Of the relevant case reports, one described two adult patients at a single institution that experienced tears in the membrane of the Berlin Heart EXCOR (BHE) pump, one that resulted in rapid cardiogenic shock due to progressive pump dysfunction [1]. The other relevant case report described the successful use of the BHE as a bridge to transplant in a 14-year-old boy that had previously had a Fontan procedure, and whose single functional ventricle was failing [2]. The patient experienced severe postoperative bleeding, and required four separate (days 15, 34, 39, and 92) pump changes for visible fibrin/thrombus. However, the patient received a successful heart transplant 179 days after the BHE was implanted and was discharged home 40 days after the heart transplant.

Qualitative Synthesis

Five articles were included in the qualitative synthesis. All five articles were [3-7] retrospective cohort studies. The studies included cohorts from the U.S. [6], Germany [5, 7], Australia [4], and the United Kingdom [3]. Four of the five studies included only pediatric patients (per CDRH definitions under 22 years of age), and one study included pediatric and young adult patients (defined respectively as under 18, and as aged 18 to 25 in that study) [4]. In the studies with only pediatric patient cohorts, median ages of patients studied ranged from 23.8 months [6] to 9.1 years [5]. Median ages were not provided in all studies [3], but the mean ages were within the aforementioned median age range. The mean age in the study that included young adults [4]was 15 years, and the age range was from 14 days to 25 years. Across all studies pediatric BHE recipients ranged in age from 3 days old[5] to 17.9 years old [7]. BHE recipients studied were implanted as early 1990 [4, 5] and as late as 2014 [4, 7].

Study Enrolling Pediatric and Young Adult Patients (n=1)

One study [4] presented outcomes for children (i.e. under 18 years of age) and young adults (i.e. 18-25 years of age) who received ventricular assist devices (VADs) at one of two hospitals in Melbourne, Australia between 1990 and 2014. Of the 64 children and young adults that received a VAD, 11 (17%) received a BHE. All BHE recipients were under 18 years old at time of implant. Other devices utilized for patient in this study included the Thoratec Para-corporeal VAD for 30 (47%) patients, the VentrAssist device from Ventracor for 14 (22%) of patients, the Medos VAD for two patients, the HeartWare VAD for three patients, the Novacor VAD for two patients, and the Jostra Rotaflow combined with Berlin Heart cannulae for 10 patients. Most safety and effectiveness results, including mortality and survival to transplant, were not presented by device type in this study. Mortality before transplant across all device types was 17% (n=11). The only outcome broken down by device type was device thrombosis. Device thrombosis was observed in 17% (n=11) of all patients: three patients implanted with the BHE, two Thoratec recipients, two VentrAssist recipients, one Novacor recipient, and one Jostra recipient. No further details regarding the outcomes of these device thrombus events were provided.

Studies Enrolling Only Pediatric Patients (n=4)

Probable Benefit

Survival rates were presented in multiple studies [3, 5-7]. On-device survival was reported in three studies [5-7] and ranged from 65% [5], for a subset of recipients in one study, to approximately 90% [7] in a different study. Survival from BHE support to transplant was reported in four studies [3, 5-7] and ranged from 61% [5] to 81% [3].

One study [3] (n=92) compared outcomes of patients that required multiple methods of mechanical circulatory support (MCS) (n=21) to patients that required only one type of MCS (n=71), but did not provide survival rates by MCS method [3]. The authors noted that BHE devices were implanted at their facility starting in 2005. Just under half of all patients needing MCS were supported with the BHE device (n=43). All twenty-one patients that required multiple methods of MCS used the BHE at least once. Survival to recovery/transplant rates were similar between patients that needed multiple MCS modalities (78%) compared to patients that needed only one MCS modality (81%), and survival to discharge was also similar between the two groups (76% vs. 72% respectively, p=0.7).

In the study from the U.S. [6], patients with single-ventricle (n=4) physiology who received a BHE were compared to patients with two-ventricle physiology (n=13) who received a BHE. Survival was similar between these two cohorts. Survival to discharge and survival to transplant were both 75% (n=3) for single-ventricle patients and 77% (n=10) for two-ventricle patients.

Another study [5] summarized the outcomes of all (n=122) patients that had received a BHE at their facility in Berlin, Germany from 1990 to 2013. The on-device mortality rate in this population was 35% (n=43). On-device mortality was also provided for subsets of patients broken down by heart failure etiology: end stage congenital heart disease (42%), heart failure after correction for congenital heart disease (61%), cardiomyopathy (27%), and myocarditis (18%). Approximately 61% of the total patient population survived to transplant (n=56) or myocardial recovery (n=18), and 4% (n=5) of the population was still relying on the device at the time of assessment.

A separate study from Germany [7] reported outcomes in pediatric patients that needed long-term MCS support and were implanted with a BHE (n=29) between 2008 and 2014. In-hospital survival for patients that received a BHE was approximately 90%, survival to transplant was approximately 66% (n=19), BHE support was ongoing in approximately 3% (n=1), and recovery was approximately 21% (n=6). It was noted in this study that one patient died unexpectedly "because of acute tamponade of the left paracorporeal pump house due to membrane defect." The authors also noted that all three BHE recipients that had single-ventricle physiology were successfully bridged to heart transplant.

Safety

Several [3, 5-7] of the studies also contained information regarding safety outcomes associated with the BHE device. In previous years, the complications most frequently observed in the published literature were neurological events, thrombosis formation, bleeding, infection, and renal dysfunction. Many of these adverse events are observed in the studies reviewed this year.

In the study that investigated outcomes in patients that required one MCS modality versus multiple MCS modalities, but did not report outcomes specifically for BHE recipients [3], patients requiring multiple MCS modalities had higher percentages of cerebrovascular attacks, major bleeding, and infection, but none of the differences were statistically significant.

The proportion of patients experiencing neurological adverse events varied greatly between studies, and the types of events reported were not consistent across studies. The percentage of patients that experienced any neurological adverse event while supported by BHE was reported in two studies [6, 7]. In one study the percentage of patients experiencing any reported neurological adverse event was approximately 10% [7] and in the other study the percentage was approximately 41% [6]. Specific neurological adverse events including hemorrhagic cerebrovascular accidents (CVAs), and thromboembolic neurological events were reported in two studies [5, 7]. Patients experiencing hemorrhagic cerebrovascular events was reported as 47% in one study [5] and 3.4% in another study [7]. The proportion of patients experiencing thromboembolic neurological adverse events were also reported in those two studies: 22% of patients in one study [5] and 6.9% of patients in the other study [7]. Anticoagulation protocols were discussed in detail in two studies [5, 7], and mentioned briefly in the other study [6]. In the German study where patients implanted with a BHE as early as 1990 [5], the authors noted that their anticoagulation protocol was modified in the year 2000. However, neurological adverse events were not broken down by time period in that study, and therefore the effect of the change in anticoagulation protocol on the occurrence of neurological adverse events could not be surmised.

Infections while on BHE support were reported in two studies [5, 7]. It was noted in one study that device-related skin infections were observed in 67% of the patients, and pulmonary infections (not reported as device-related) were observed in 23% of patients [5]. In a separate study [7] skin infections around the cannulae were reported in 10.3% of BHE recipients and 3.4% (n=1) of BHE recipients had a subcutaneous abscess form close to the aortic cannula.

Thrombosis formation was reported to necessitate pump change in 31% of patients (n=9) in one study [7]. Thrombus formation in the BHE pump was noted as the main reason for pump exchange in another study [5], but the percentage of BHE patients needing a pump exchange due to thrombus formation was not provided. While renal dysfunction was a noted adverse event from the 2015 literature review, none of the studies reviewed in 2016 presented proportions of patients with renal dysfunction while on BHE support.

Discussion

The review of the literature for the BHE reported probable benefits. The use of the BHE appears to be associated with a relatively high rate of survival while the patient is on-device and survival from BHE support to transplant. In each study reporting overall pediatric survival on BHE, the majority of BHE recipients survived to discharge or transplant. Additionally, probable benefits, including relatively high survival rates, were observed in population subsets that may have more inherent risk (patients with multiple MCS modalities needed, and patients with single-ventricle physiology). In one study, higher on-device mortality proportions were observed in BHE pediatric patients with congenital heart disease (end stage or after prior surgical treatment for) as the etiology of heart failure in comparison with pediatric patients with cardiomyopathy or myocarditis as the heart failure etiology. However, previously observed device-associated risks, were also noted from this literature review. The device-associated risks observed included: neurological events, thrombosis, and infection. A higher proportion of patients experienced adverse events if they required multiple modalities of MCS when compared to patients that only needed one modality of MCS. However, those results were not statistically significant, and survival and transplantation rates were similar between the groups. While not frequently observed, pump membrane rupture was noted as a potential safety issue in one case report and in one of the retrospective cohort studies. Specifically, a membrane rupture resulted in rapid cardiogenic shock in an adult patient in the case report [1], and a membrane malfunction resulted in a child's death in the cohort study [7]. It should be noted that both of those cases of membrane rupture occurred in Europe where a different pump membrane is approved for use. Overall, the reported safety events appeared similar to those observed in previous years and are consistent with events reported in MDRs received.

This literature review had several limitations. All of the studies in the qualitative synthesis were retrospective studies. Only four studies presented survival proportions or adverse event proportions for pediatric patients supported by BHE. The adverse events summarized varied greatly from study to study. Sample sizes appear to have been smaller than those of studies from previous years, and several of the current studies were populations drawn from single institutions. None of the studies presented data for BHE supported pediatric patients between the ages of 18 and 22.

OVERALL CONCLUSION

The FDA has monitored and reviewed data regarding the EXCOR since its HDE approval in December 2011. No new or unexpected risks, in reference to the premarket and post-market data evaluations for the pediatric population, are noted in our review of published literature and MDRs. Therefore, based on information currently available to the FDA, the Berlin Heart EXCOR PVAD device does not pose an unreasonable or significant risk of illness or injury, and the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

1. Sousa Casasnovas, I., et al., *Two Different Sites of Membrane Rupture in the Berlin-Heart EXCOR Ventricular Assist Device.* Rev Esp Cardiol (Engl Ed), 2016. **69**(5): p. 525-7.
2. Halaweish, I., R.G. Ohye, and M.S. Si, *Berlin heart ventricular assist device as a long-term bridge to transplantation in a Fontan patient with failing single ventricle.* Pediatr Transplant, 2015. **19**(8): p. E193-5.
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.

Appendix 1: Current Health Status and Pediatric Stroke Outcome Measure Scores for Study Subjects who were Successfully Weaned or Transplanted

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 of 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 on own. Significant improvement in language development.
Weaned	40	Parents refused testing					24 month post: Needs help with most things and unable to ambulate

Appendix 2: Functional Assessment Summary Tables

Pediatric Evaluation of Disability Inventory (PEDI)

Domain	Baseline		12 month post explant		24 month post explant		Change Baseline to 12 month post		Change Baseline to 24 month post	
	N	Median [IQR]	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]
FUNCTIONAL SKILLS										
Self-care	8	45.7 [27.6 , 50.5]	11	39.4 [33.6 , 44.1]	9	34.8 [28.3 , 41.1]	6	-5.8 [-8.0 , 9.2]	3	5.6 [-19 , 19.1]
Mobility	8	34.8 [27.8 , 41.1]	10	37.8 [18.9 , 45.9]	8	34.8 [28.0 , 49.3]	5	-5.2 [-10 , 4.9]	2	-7.9 [-8.7 , -7.0]
Social Function	11	42.5 [21.1 , 54.1]	11	38.4 [29.5 , 43.2]	10	36.4 [26.7 , 46.8]	6	-11.6 [-25 , 8.2]	5	4.3 [-17 , 4.9]
CARE GIVER ASSESSMENTS										
Self-care	12	39.4 [37.9 , 44.9]	9	40.8 [35.2 , 58.9]	9	35.7 [32.6 , 56.2]	5	-0.3 [-0.5 , 1.1]	4	-2.1 [-11 , 13.1]
Mobility	11	32.9 [16.2 , 33.3]	9	36.9 [31.8 , 44.5]	9	39.7 [27.9 , 44.9]	5	7.5 [6.2 , 15.6]	4	7.6 [-3.4 , 28.2]
Social Function	12	46.3 [41.9 , 56.2]	10	40.1 [32.5 , 47.0]	9	49.7 [44.1 , 56.5]	7	-16.8 [-23 , -0.2]	4	13.8 [1.9 , 24.5]

Functional Status II (FSII)

Score	Baseline		12 month post explant		24 month post explant		Change Baseline to 12 month post		Change Baseline to 24 month post	
	N	Median [IQR]	n	Median [IQR]	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]	17	82.1 [75.0 , 82.1]	16	16.1 [3.6 , 25.0][2]	13	17.9 [3.6 , 28.6][2]
Total Within age group	28	68.6 [50.0 , 76.7]	20	79.5 [74.7 , 91.2]	17	82.4 [70.8 , 84.3]	16	15.0 [1.0 , 24.5][2]	13	15.7 [2.3 , 23.5][2]
General Health	28	65.0 [47.1 , 75.0]	20	76.5 [73.5 , 91.4]	17	82.9 [68.6 , 85.7]	16	12.5 [2.3 , 27.1][2]	13	17.1 [-5.0 , 28.6][2]
Responsiveness/ Activity/ Interpersonal Functioning[1]	28	71.4 [60.4 , 76.0]	20	78.6 [71.4 , 85.0	17	67.9 [64.3 , 78.6]	16	7.1 [0.0 , 14.1][2]	13	2.5 [-3.6 , 14.0]

[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

Appendix 3: Quality of Life Assessment Summary Table

Pediatrics Quality of Life (PedsQL)

Scale	Baseline		12 month post explant		24 month post explant		Change Baseline to 12 month post		Change Baseline to 24 month post	
	n	Mean ± Std [Range]	n	Mean ± Std [Range]	n	Mean ± Std [Range]	n	Median [IQR]	n	Median [IQR]
PARENT PROXY	Note: only 19 of 39 subjects were ≥ 2 years old at enrollment									
Total Scale Score	15	46.9 ± 19.1 [20.2, 76.1]	17	72.7 ± 24.5 [23.9, 100.0]	18	73.4 ± 16.2 [46.7, 100.0]	8	24.0 [5.4, 35.3][2]	6	21.9 [7.8, 42.2][2]
Psychosocial Health[1]	15	51.3 ± 18.3 [25.0, 87.5]	17	76.5 ± 21.8 [36.7, 100.0]	18	73.9 ± 13.6 [45.0, 100.0]	8	17.5 [8.3, 31.7][2]	6	27.7 [16.3, 48.8]
Physical Health	16	38.1 ± 26.6 [6.3, 87.5]	17	67.3 ± 33.2 [0.0, 100.0]	18	73.4 ± 22.9 [31.3, 100.0]	8	21.9 [7.8, 42.2]	6	25.8 [15.0, 35.0][2]
CHILD SELF REPORT	Note: only 14 of the 39 subjects were ≥ 5 years old at enrollment									
Total Scale Score	3	51.8 ± 25.1 [28.3, 78.3]	8	74.2 ± 13.1 [44.6, 84.8]	6	75.2 ± 11.4 [54.3, 88.0]	1	n/a	1	n/a
Psychosocial Health[1]	3	56.7 ± 23.3 [30.0, 73.3]	8	70.4 ± 9.3 [51.7, 81.7]	6	72.2 ± 9.0 [60.0, 85.0]	1	n/a	1	n/a
Physical Health	3	42.7 ± 39.1 [15.6, 87.5]	8	81.3 ± 23.4 [31.3, 100.0]	6	80.7 ± 21.2 [43.8, 100.0]	1	n/a	1	n/a

[1]Psychosocial Health = Psychosocial Health Summary Score which is a combination of Emotional, Social and School functioning

[2] Wilcoxon test significant $p<0.05$