FDA Executive Summary

Prepared for the
Fall 2020, Meeting of the
FDA's Pediatric Advisory Committee

H150003

Flourish™ Pediatric Esophageal Atresia Device

Contents

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience since the 2019 Pediatric Advisory Committee (PAC) update. The current reporting period is December 2018 through May 2020. The purpose of this review is to provide the PAC with postmarket 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 executive summary will include postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

II. INDICATIONS FOR USE

The Flourish™ Pediatric Esophageal Atresia Device is indicated for use in lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a tracheoesophageal fistula (TEF) or in pediatric patients up to one year of age for whom a concurrent TEF has been closed as a result of a prior procedure. This device is indicated for atretic segments < 4 cm apart.

The indication for use statement has been modified from that granted for the Humanitarian Use Device (HUD) designation. The HUD designation was "for lengthening atretic esophageal ends and creating an anastomosis with a non-surgical procedure in pediatric patients, up to one year of age with esophageal atresia without a currently existing tracheoesophageal fistula, or for whom a concurrent TEF has been closed as a result of a prior procedure." It was modified for the Humanitarian Device Exemption (HDE) approval to include the device trade name and specify that atretic segments must be < 4 cm apart.

DISEASE CONDITION

Esophageal atresia (EA) is a developmental arrest of the esophagus resulting in the absence of normal esophageal lumen. The overall incidence of EA/TEF ranges from 1/2500 to 1/4500 live births. Five types of EA, with and without concurrent TEF, are recognized (Figure 1). Infants usually present with excessive oral secretions, feeding intolerance, and/or respiratory difficulties which necessitates suctioning and feed through gastrostomy tube. Morbidity/mortality is dependent on associated conditions; EA/TEF are conditions commonly found in patients with VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, limb) and CHARGE association (coloboma, heart, atresia, choanal, retarded growth, genital hypoplasia, ear deformities).

Current standard of care includes surgical repair via thoracotomy or thoracoscopy to create an anastomosis. If this is unsuccessful, colonic, gastric, or jejunal interposition are options.

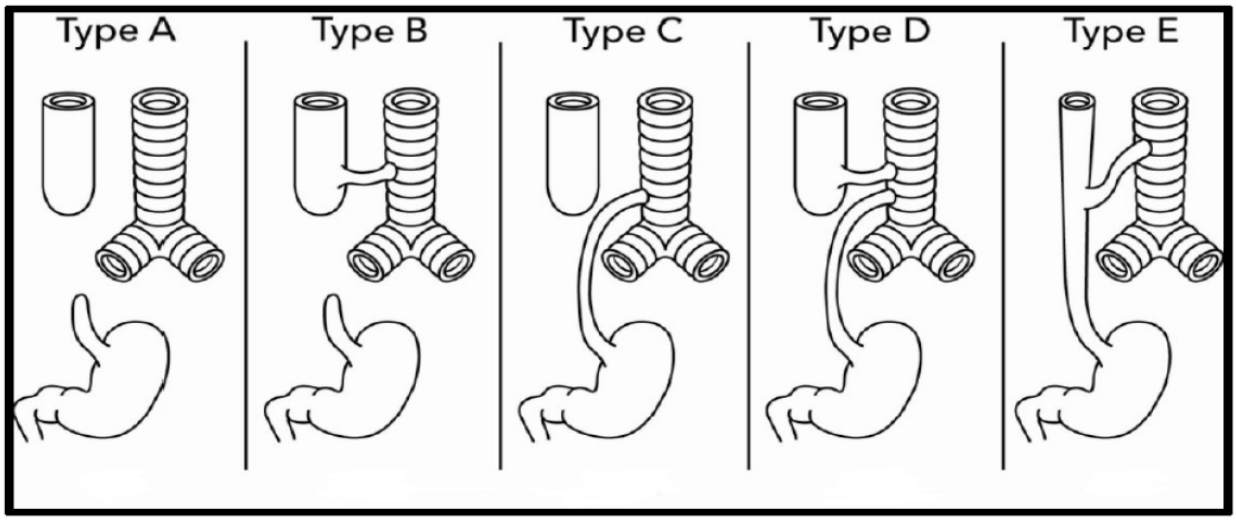


Figure 1: Types of Atresia

III. BRIEF DEVICE DESCRIPTION

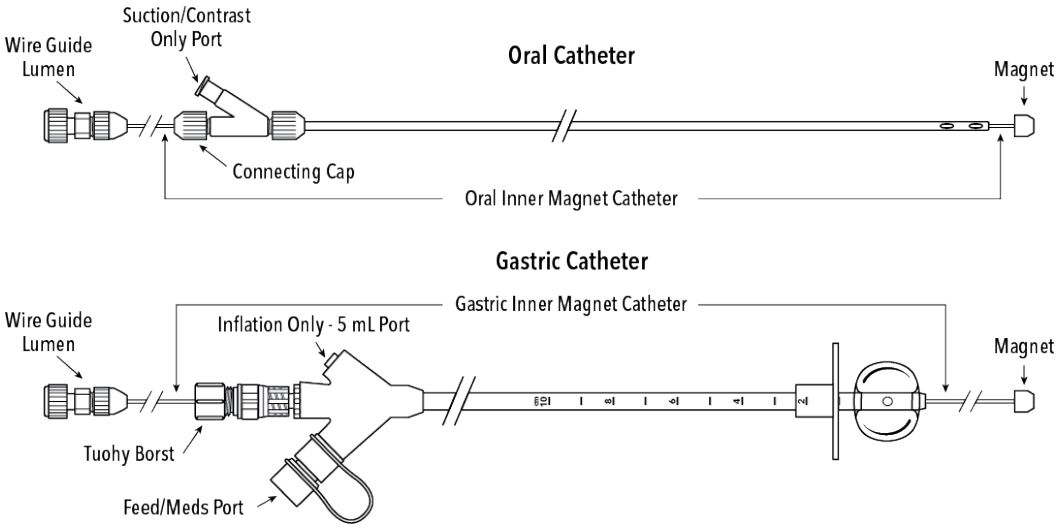
The Flourish™ Pediatric Esophageal Atresia Anastomosis Device consists of an oral/esophageal catheter and a gastric catheter. The oral/esophageal catheter is a 10 Fr two-lumen catheter. One lumen is for injection of contrast to confirm anastomosis and suction of saliva; the other is for a wire guide.

The gastric catheter is a modified two-lumen 18 Fr/ 5 cc balloon retention catheter. One lumen is for balloon inflation/deflation. The second lumen is modified by the addition of the gastric magnet catheter, essentially creating a lumen within a lumen. This modified arrangement allows for initial placement of a wire to guide introduction of the gastric magnet catheter assembly. Once the wire guide is removed from the gastric magnet catheter, flushing can occur through this created lumen or through an added accessory lumen.

Feed is delivered through the original accessory feed port adjacent to the adapted central port. The inflated balloon holds 5 ml of liquid.

The distal end of each of the internal catheters is fitted with a bullet-shaped neodymium iron boron (NdFeB) magnet, which features a central hole for insertion of up to a 0.038-inch guide wire. When the two catheters are aligned tip to tip the magnets have opposite polarities; thus attracting each other. They are “bullet” shaped and have a diameter of 6.35 mm. Each magnet catheter is 56.5" in length. Figure 2 illustrates the complete device.

Figure 2- Flourish™ Pediatric Esophageal Atresia Anastomosis Device:



Principles of Operation

In a candidate infant, the distance between the atretic segments is assessed under fluoroscopy using radiopaque flexible catheters and metal probes. After identification of the pouches, the oral/esophageal catheter is inserted orally and advanced until the magnet is located at the distal end of the upper pouch. The gastric catheter is inserted over a wire guide, under fluoroscopy through a mature stoma and advanced until the magnet is located at the distal end of the lower pouch. The gastric catheter is secured to the stomach wall internally with a balloon and externally with a bolster (Figure 2 - Flourish™ Pediatric Esophageal Atresia Anastomosis Device Placement, below).

Within three to thirteen days, the traction caused by the magnets allows the esophageal sacs to approximate. Daily biplane chest radiographs are taken to assess the distance between magnets. Once approximated, the surrounding tissues grow together while the tissue between the magnets undergoes necroses, causing development of an anastomosis, thereby creating a connected passage from mouth to stomach.

Once an anastomosis has been confirmed through fluoroscopy, the magnets are removed. The proximal end of the oral/esophageal inner magnet catheter is cut. A new wire is introduced through the oral/esophageal inner magnet catheter through the newly formed anastomosis and exits through the gastrostomy port. The oral/esophageal catheter is pushed distally toward the stomach until magnets are in the stomach, below the anastomosis. Then, the oral/esophageal inner magnet catheter is gently pushed, and the gastric catheter is pulled until the system exits from gastrostomy site, thus removing the gastrostomy tube, oral/esophageal and gastric inner magnet catheters, and the magnet pair as a unit. A new orogastric tube or nasogastric tube is placed for one to three days.

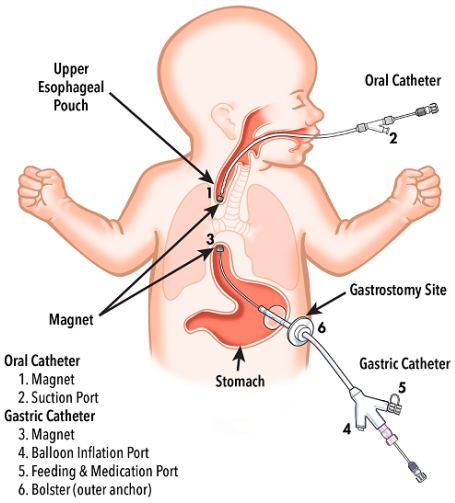


Figure 3 Device Illustration

IV. REGULATORY HISTORY

Flourish™ Pediatric Esophageal Atresia Device received designation as a HUD Designation on October 28, 2010, and on May 12, 2017, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the FDA.

Table 1 below provides a timeline of relevant regulatory decisions and events:

Event	**Date of occurrence or FDA approval**
HDE Approved	May 12, 2017
Post-approval study (PAS) protocol approved	April 27, 2018
First post-approval patient implanted with Flourish™	November 2018
Post-Approval Study (PAS) Annual Report reporting that of the first 4 PAS subjects, 3 subjects failed to achieve anastomosis	July 2019
HDE Supplement for PAS protocol changes for physician training of measuring gap and other minor protocol changes	October 9, 2019
HDE Supplement to implement labeling change regarding measuring gap	October 25, 2019

HDE Clinical Data

The HDE application was approved based on a total of 16 patients whose case studies were obtained from literature as well as compassionate/emergency use cases submitted to the FDA.

FDA relied upon two articles from the literature[1,2]. In the article entitled, "Magnetic gastrointestinal anastomosis in pediatric patients," by Zaritzky et al., there were nine patients with previously untreated esophageal atresia who were treated by magnetic compression anastomosis at a single center in Argentina. The gap between the upper and lower pouches was evaluated by placement of metal probes viewed on anterioposterior (AP) and lateral chest x-rays. Only children with a gap of 4 cm or less between the esophageal and gastric pouches were treated with the catheter-based device. All nine patients achieved anastomosis. However, eight of the nine patients developed anastomotic strictures that required dilatation and two of these patients with intractable esophageal stenosis also underwent placement of 10 mm diameter fully covered biliary stents after dilatation. One patient (who underwent several dilatations and stent placement) ultimately required surgical re-anastomosis.

There were two cases described in the article, "Staged repair of esophageal atresia: Pouch approximation and catheter-based magnetic anastomosis," by Lovvorn et al. In both patients, anastomosis was achieved, but for one patient experienced anastomosis and the patient was swallowing oral secretions well but four months had persistent stenosis likely related to the fibrotic healing response of the salivary leak that complicated the original suture-approximation procedure.

For the remaining patients, FDA relied upon information submitted in five emergency use case reports. Of those patients, one had to undergo serial dilations and at a year and a few months, had a recalcitrant stricture, one required multiple dilations and 3 months post anastomosis was receiving training in swallowing and speech, one had no further treatment due to need for ventilator support for a pre-existing congenital anomaly, one had serial dilations and a subsequent esophageal stent, and one required surgery to correct an undiagnosed TEF.

The two literature reports provided data from 11 patients, and the emergency use case reports provided data from five patients, resulting in 16 total patients. All 16 patients achieved anastomosis, but 13 of the patients developed anastomotic strictures that required balloon dilation and/or esophageal stenting. This stricture rate is higher than what was reported for standard of care

[1] Zaritsky M. Ben R. Johnston K. Magnetic gastrointestinal anastomosis in pediatric patients. J Ped Surg. 2014. 49:1131-1137.
[2] Lovvorn H, Baron M, Danko M, et al. Staged repair of esophageal atresia: Pouch approximation and catheter-based magnetic anastomosis. J Ped Surg Case Reports. 2014; (2): 170-175.
[3] Lévesque, D., et al. Refractory strictures post-esophageal atresia repair: what are the alternatives? Dis Esophagus. 2013 May-Jun;26(4):382-7.
[4]Pinheiro, PF., et al. Current knowledge on esophageal atresia. World J Gastroenterol. 2012 Jul 28;18(28):3662-72.

surgical repair that is estimated to be 30 to 40%[3,4]; however, anastomotic repair could occur earlier with the device, and avoid several surgical complications. Therefore, it is was concluded that probable benefits of earlier anastomotic repair and fewer surgical complications outweighed the risks higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient.

Labeling Update
Of note, an important labeling change was made in a Supplement approved in October of 2019 to correctly measure the atretic gap in candidate infants, so that the device could be successfully used as intended (see more details below).

V. POSTMARKET DATA: DEVICE USE NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual (n=1).

As stated in section 520(m)(8) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

It was reported in information provided to FDA in preparation for the Pediatric Advisory Committee meeting that 33 devices were sold in the reporting period, well below the 8,000 device ADN requirement. The 33 devices sold includes those that were returned to the Sponsor unused. There were no devices sold prior to this reporting period.

The table below provides the number of devices sold and used during the current reporting period of November 2018 through May 2020.

Table 2. Device Use

Reporting Period	Total Sales	Total Implanted	Patients in Post Approval Study (PAS)
Nov 2018 – May 2020	33	20*,**	6**

*Of the 20 devices implanted, 5 patients were treated outside the U.S. (Canada). These patients were not enrolled in the PAS.

**In two patients the device was used in two separate procedures. However each patient was counted once.

VI. POSTMARKET CLINICAL DATA

Given the limited amount of clinical information provided and relied upon for safety and probable benefit for approval of the HDE as well as a post-procedure stricture rate that was higher than that of standard of care surgical repair, a PAS was put into place to obtain longer term data on these events.

PAS Protocol

The Flourish™ device was approved on May 12, 2017 with a condition of approval to conduct a PAS. After interaction with FDA, the PAS study protocol was approved on April 27, 2018. Consistent with the condition of approval, the study requires the following:

- Prospective, single-arm, new enrollment observational study
- 15 sites, at least one U.S. site
- A minimum of 20 subjects
- 2 year follow-up
- Primary endpoint: Safety (stricture at the anastomotic site leading to the need for dilation or surgery, peri-anastomotic leaks, adverse events possibly, probably, or causally related to the device or procedure)
- Secondary endpoint: Successful anastomosis formation, defined as creation of a lumen connecting the upper esophageal pouch to the lower esophageal pouch as demonstrated by union of the device magnets and an esophagram showing connected flow of contrast agent.

For the first two years following approval, Cook is required to submit annual reports every 6 months. To complete the PAS study, Cook estimated that one patient would be enrolled per month in the PAS. Rate of enrollment was based on expected device use rate with the expectation that not all would agree to enroll. However, in the most recent annual report, Cook reported that this expectation has not been met.

In the section below, we first describe the interim results from the PAS and then briefly describe available outcome data for the patients that were not enrolled in the PAS. A high-level overview of the post-approval data is provided in Table 3. As seen in the table below, there were a total of twenty patients implanted with the Flourish™ device after approval of the HDE; six of the patients enrolled in the PAS study and thirteen of the patients did not enroll in the PAS study. Two out of six patients enrolled in the PAS study achieved anastomosis (see shaded rows), and eight out of fourteen of the patients not enrolled in the PAS study achieved anastomosis.

Table 3: Overview of PAS and non-PAS enrolled outcomes

Patients (in chronological order)	PAS?	Anastomosis Achieved?
1	Yes	No
2	Yes	No
3	Yes	Yes

4	No	No
5	Yes	No
6	No	Yes
7	No	Yes
8	No	Yes
Labeling Changes Implemented – October 2019		
9	No	Yes
10	Yes	No
11	No	No
12	No	No
13	No	No
14	Yes	Yes
15	No	Yes
16	No	Yes
17	No	No
18	No	Yes
19	No	No
20	No	Yes

PAS Study Status

The following information is based on the most recent May 2020 PAS annual report and information provided interactively from December 2019 through May 2020.

Per the current information, six patients were enrolled in the post-approval study and treated with the Flourish™ device. Interim post-approval study results show that two patients achieved a successful anastomosis and four patients did not achieve an anastomosis.

The first patient had Type C esophageal atresia (previously repaired distal TEF). Twenty-five days prior to device placement, fistula ligation was completed, and a radiographic exam showed an atretic gap of 3.9 cm. The method of determining the gap was noted as follows, "gap study (using clip on distal esophagus and OE [oral esophageal] tube and contrast in proximal) ." This measurement prior to magnet implementation did not entail tubes in the distal esophagus. Based on the available information, the patient met the study eligibility criteria and was enrolled. At completion of the study procedure, the Flourish™ magnets were in the distal-most portion of each esophageal end. Following device placement, radiographic imaging was performed to confirm placement of the magnets; however, at this time the atretic gap was observed to be > 4 cm.

One day post-procedure, the oral catheter was repositioned from the mouth to the nares. Two days post-procedure, a chest X-ray was performed, and the magnets were reported to be 4.8 cm apart. Ten days post-procedure, the Flourish™ device was removed; anastomosis was not achieved. On the same day, the patient underwent thoracotomy with repair of the esophageal atresia and exited the study.

The second patient had Type C esophageal atresia (previously repaired TEF). Sixty-four days pre-procedure, the patient underwent transsternal ligation of the fistula, cardiac surgery via median sternotomy, thymectomy, hypothermic cardiopulmonary bypass, repair of total anomalous pulmonary venous return, ligation of patent ductus arteriosus, and partial closure of atrial septal defect. The initial atretic gap was measured at 2 cm. At the completion of the study procedure, the Flourish^{TM} magnets were in the distal-most portion of each esophageal end. The magnets were repositioned on three different occasions due to migration of the ends of the magnets (further apart). On one occasion, the oral catheter was moved from the mouth to the nares. After no further progress of movement of the magnets toward each other and an inability to achieve anastomosis, the device was removed 13 days post-procedure. Sixty-nine days post-procedure, the patient underwent thoracotomy with esophageal repair/anastomosis and exited the study.

The third patient had Type C esophageal atresia (previously repaired TEF). One hundred eight days pre-procedure, the patient underwent a right thoracotomy with temporary vessel loop around the gastroesophageal junction through an upper midline incision. The fistula was unable to be located due to adhesions. A gap study performed in the operating room before device placement measured the gap at 1 cm. The Flourish^{TM} device was placed and at completion of the study procedure, the Flourish^{TM} magnets were in the distal-most portion of each esophageal end. Due to stricture, balloon dilation of the gastroesophageal junction was also completed during the Flourish^{TM} device placement procedure. An anastomosis was achieved and confirmed by esophagram 4 days post-procedure, which showed connected flow of contrast agent. The device was removed 6 days post-procedure. Following review of the medical chart 18 days post-procedure, it was reported that the patient had undergone dilation for stricture at the anastomotic site 13 days post-procedure.

The fourth patient had Type A esophageal atresia (without TEF). The patient had no prior thoracic surgical interventions. Using retrograde rigid esophagogastroscopy with fluoroscopy and a radiologic measuring tape, the site measured the initial atretic gap at 3 cm. At completion of the study procedure, the magnets were in the distal-most portion of each esophageal end. Three days post-procedure, the patient returned to the operating room, since there had been no movement of the magnets toward each other and the orientation had changed. The catheters were reoriented with tension on the catheters. The gap measured less than 4 cm; however, the site noted that the magnets did not seem to attract to each other at rest. Six days post-procedure, the patient returned to the operating room, since no progress was made, and the magnets had not aligned well. Endotracheal tubes were placed over each magnetic catheter for improved mechanical traction and a guidewire was left in place in the lower (gastric) catheter for additional cephalad direction.

Nine days post-procedure, the patient returned to the operating room and underwent rigid gastroscopy and right muscle-sparing thoracotomy with mediastinal exploration and pexy of esophageal ends. As noted in the operative report: “We proceeded to the operating room today with hopes of mobilizing each end of the esophagus to bring them closer together such that the magnets would be able to detect each other and provide sequential advancement of the esophageal ends.” The esophagus was found to share a common wall with the trachea and sharp dissection of the common wall was attempted. The proximal esophageal pouch was noted to be

very high in the mediastinum and full dissection from the trachea was not achieved. The distal esophageal pouch was found to be short as viewed through the chest (thoracotomy), "perhaps 1 cm". Traction sutures were placed on the ends of both esophageal pouches. The Flourish™ device was removed as the magnetic ends of the Flourish™ device were unable to detect each other (inability to achieve anastomosis).

This patient died 40 days post-procedure. In addition to esophageal atresia, the patient had a history of trisomy 21, low ears, duodenal atresia, ventricular septal defect, and patent ductus arteriosus. The cause of death was reported as "hypovolemic shock in setting of postnatal hydrops in setting of complicated trisomy 21 with EA." The patient had "worsening hypotension despite maximizing support and development of multi-system organ failure (including respiratory failure, oliguria and then anuria- kidney failure, GI failure)." The parents elected to compassionately discontinue ventilator support. The investigator reported the death as unrelated to the study device and study procedure.

The fifth patient had Type C esophageal atresia with distal TEF. There were no other comorbidities noted. The patient had undergone previous surgery for fistula ligation with mobilization and dissection of the esophageal ends. The length of the initial untreated gap measured 5 cm. On the day of the procedure, the length of the gap to be bridged measured 3 cm by "fluoro measurement in OR with ngt (nasogastric) and catheter distally."

The device was placed under general anesthesia. The magnets were in the distal most portion of the esophageal ends at the completion of the procedure. The resulting esophageal gap (after device placement) measured 2.7 cm. No additional procedures were performed. Sixteen days post-procedure, the Flourish™ Device was removed. Anastomosis was not achieved. It was noted that the patient "required multiple adjustments and magnets did not come together during 2 weeks." Forty-two days post-procedure, the patient exited the study to undergo subsequent treatment to correct the esophageal atresia.

It was suspected that the previous surgery, and/or the question of perforation of the proximal esophageal ends, resulted in scarring around the ends that did not allow them to lengthen with the magnets, resulting in an unsuccessful anastomosis.

The sixth patient had a Type C EA (previously repaired TEF). On pre-procedure day 81, the patient underwent a rigid bronchoscopy, TEF ligations, failed esophageal anastomosis, pexy of upper and lower esophageal segments to prevertebral fascia, and chest tube placement. On pre-procedure day 77, the patient underwent a right thoracotomy for repair of the esophageal leak (upper esophageal pouch). The initial untreated atretic gap measured 2 cm. The measurement was taken with a radiopaque ruler, with an enteric tube in the upper pouch and a gastrostomy tube in the lower pouch. The Flourish™ device was placed and at the completion of the placement, the Flourish™ magnets were in the distal-most portion of each of the esophageal ends. The resulting gap measured 2 cm. An anastomosis was achieved 11 days post-procedure, and the Flourish™ device was removed 12 days post-procedure. Anastomosis was endoscopically confirmed at removal. Following review of the medical chart, it was reported that the patient had undergone dilation for stricture at the anastomotic site 26 days post-procedure. On post-procedure day 40, a scheduled dilation was attempted but unsuccessful. A guidewire

was unable to be passed using fluoroscopy. On post-procedure day 54, a second Flourish™ device was placed for treatment of the esophageal stricture. An anastomosis was achieved 4 days post-procedure and was confirmed by esophagoscopy and fluoroscopy.

Root Cause Analysis

Following the fourth patient enrolled in the PAS, Cook submitted their regularly scheduled annual report to FDA. Because three of four post-approval study patients had not achieved anastomosis following placement of the Flourish™ device, Cook investigated potential causes for these failures, evaluating device specifications and pre-procedure imaging used to assess the atretic gap.

Nonclinical testing confirmed that the device specifications, such as magnet strength, remain consistent with pre-approval devices used in the clinical setting and that supported HDE approval.

Clinical experience from compassionate and emergency uses of the device suggested that the chance of successful anastomosis would be decreased if the atretic gap was more than 4 cm. In collaboration with a physician consultant with experience in device use and imaging techniques, Cook determined that verification of an atretic gap of no more than 4 cm, as required by the intended use, needed to be confirmed immediately prior to placing the device as stated in the current labeling.

Review of imaging suggested that a standard measurement technique was not being applied by physicians to measure the atretic gap and subsequently determine a patient's study eligibility. In some cases, the atretic gap may have been underestimated (e.g., artificially shortened by use of rigid tools under tension). In light of this, Cook clarified that they intended to provide physicians enhanced recommendations recommending that flexible tools (e.g., feeding tube, flexible catheter, floppy tipped wire guide) be used in imaging to assess the atretic gap, and that both lateral and anteroposterior (AP) views be provided.

Labeling Modification

As a follow-up to Cook's initial PAS results and their root cause analysis, FDA requested labeling modifications to address the risk of inaccurate atretic gap measurement. Cook proposed the following labeling modifications for the Instructions for Use and Power Point Training presentation required for Physicians

- To determine if a patient is a suitable candidate for Flourish™ placement, an accurate measurement of the esophageal gap needs to be made. The following imaging recommendations should be followed:
    - It is essential that the measurement be made by not exerting any pressure over the esophageal pouches to approximate the atretic gap.
    - To not exert any pressure, it is better to use radiopaque flexible catheters under fluoroscopic visualization. Radiographs should be taken in AP and lateral incidences. It is also necessary to include a radiopaque ruler in the field of view.
    - Rigid probes are an alternative to the use of flexible catheters, but in this case, special attention should be taken not to push the probes to artificially reduce the gap distance.

- Before starting the catheter placement procedure, the distance between upper and lower esophageal pouches must be measured and determined to be less than 4 cm in length, without exerting pressure to the pouches in AP and lateral fluoroscopic views.

FDA approved these labeling changes in October 2019 based on the presumption that they would address the anastomotic failures that were observed in initial PAS results.

Anastomosis Outcomes in Non-PAS Patients

In addition to the six PAS patients discussed above, as of May 31, 2020 there were fourteen treated that were not enrolled in the PAS study. Cook informed FDA that centers were typically unwilling to participate due to their expected costs exceeding reasonable compensation, or because the necessary study processes were considered too burdensome to justify for a single case.

Of the fourteen patients not enrolled in the study, eight were reported to have formed an anastomosis. There is limited clinical information on these patients as they were not enrolled in the PAS study.

Conclusions

In Summary, a total of twenty patients were treated; 6 PAS patients and 14 non-PAS patients. Of the 6 PAS patients, only 2 achieved anastomosis. Of the 14 non-PAS patients, eight achieved anastomosis.

This post-market rate of anastomotic success (50%, 10/20) is half of the rate seen (100%, 16/16) in the cases evaluated for HDE approval. This may be partially due to measuring technique, as the Sponsor proposed. Other reasons may include scarring of the esophageal ends from previous intervention, age of the patient, site where the procedure was performed, atresia type, and/or physician experience. However, the limited data does not allow for definitive conclusions. Even with this reduced rate, FDA still finds it reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury. This includes consideration of the probable risks and benefits of alternative forms of treatment. With the Flourish™ device, anastomotic repair can occur earlier than a thoracotomy and avoids several surgical complications. This is especially important for a condition that is usually co-existent with other potentially serious comorbidities. In these cases, potential benefit of device use to provide a less invasive approach and avoid a major surgical procedure would outweigh the risks.

It is unclear why the rate of anastomosis trends higher in the non-PAS patients than those that were enrolled in the PAS study. Further data collection and analysis is warranted to better understand factors that lead to anastomosis success.

Regarding post-procedure stricture rate, of the two PAS patients who formed an anastomosis, a stricture also developed at the anastomotic site in two patients. In one patient, this occurred at 13 days post procedure and required dilation. The other patient also underwent dilation for a stricture at the anastomotic site 26 days post-procedure.

Due to the limited information on the non-PAS patients, it is unclear if and/or how many patients developed a post-procedure stricture. This information was not available as of May 31, 2020.

VII. Systematic Literature Review on the Safety and Probable Benefit of Flourish™ in the Pediatric Population

Purpose

To conduct a systematic literature review on medical literature that evaluates the safety and probable benefit of the Flourish™ device for esophageal atresia with or without tracheoesophageal fistula in pediatric patients.

Methods

On July 13, 2020, a search was conducted using the PubMed and Embase databases with the following search terms and strategies:

> (Flourish™ OR magnet*) AND ("esophageal atresia" OR (“trachea-esophageal fistula” OR “tracheoesophageal fistula” OR TEF) OR “magnetic compression anastomosis” OR “short gap atresia”)

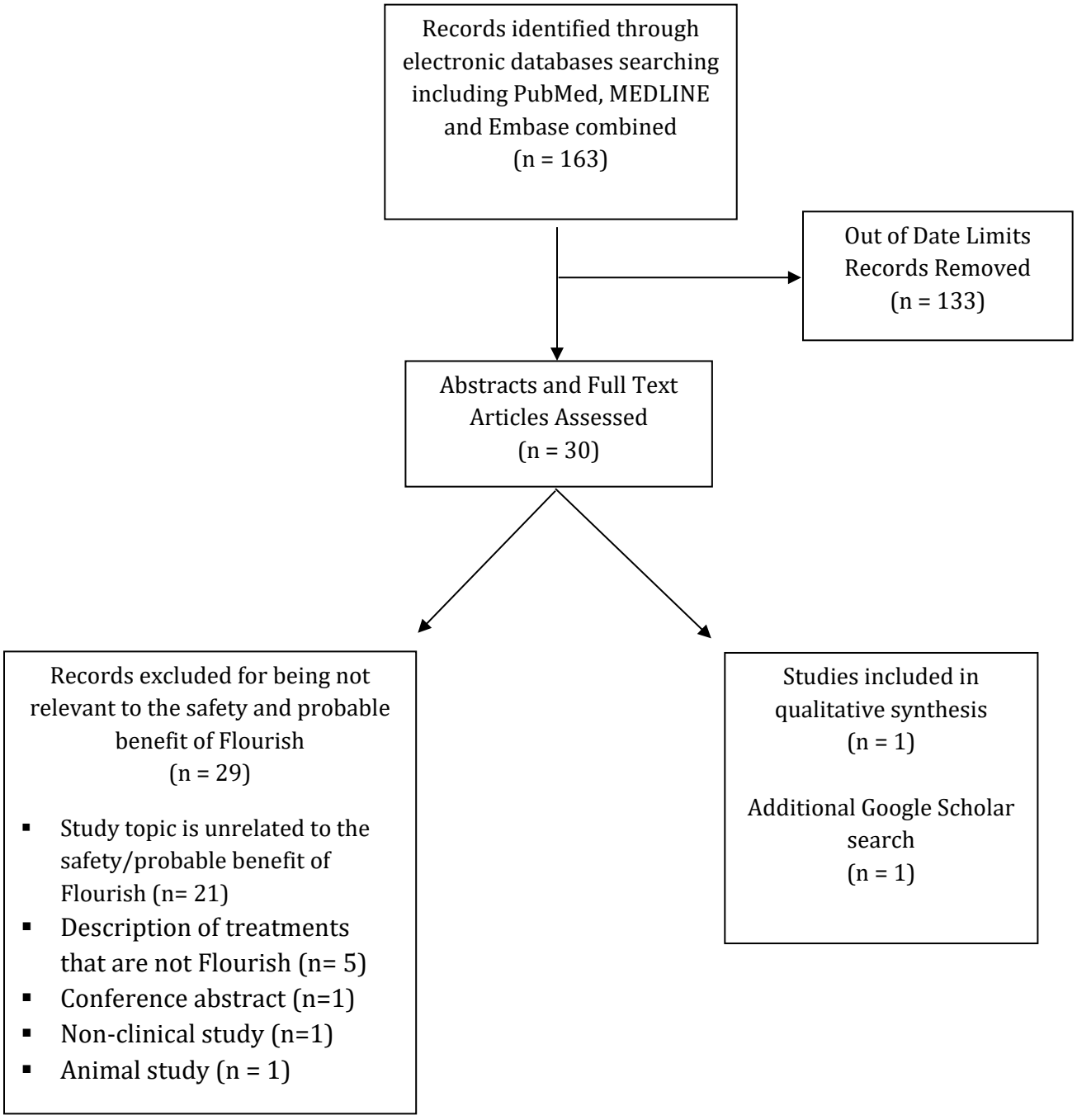
Because the 2019 PAC update included a literature search up to November 30, 2018, the current search was restricted to articles published between December 1, 2018 and May 31, 2020 in humans. To determine the eligibility of the articles for inclusion, the titles and abstracts were first screened, and then relevant full text articles were screened, selected, and reviewed for data extraction and synthesis.

Results

Our search strategy resulted in a total of 163 articles from PubMed, MEDLINE and Embase combined. After filtering by the date limits, 133 articles were excluded and 30 remained for full text article review. After full texts were reviewed, all but one article were excluded because they did not provide information on the safety and probable benefit of Flourish™ for the treatment of esophageal atresia. Figure 4 below shows the flow diagram for the literature search.

An additional article as the one selected with a similar title and with the same senior author (Zaritzky M) was found using Google Scholar. This article is a single case report. Although it was published in September 2018, it is included in this review because it was not available in the 2019 reporting period literature search. Summaries of these two articles are included below.

Figure 4: Flow diagram of the articles retrieved and study selection.



Slater B J, Borobia P, Lovvorn HN, Raees MA, Bass, KD, Almond S, Hoover JD, Kumar T, Zaritzky M (2019) Use of magnets as a minimally invasive approach for anastomosis in esophageal atresia: Long-term outcomes. Journal of Laparoendoscopic and Advanced Surgical Techniques, Vol 19, Issue 10, Pages 1202 – 1206, DOI: 10.1089/lap.2019.0199, ISSN: 1557-9034 1092-6429.

Summary

The purpose of this study was to report long-term outcomes for the use of magnets in 13 patients with EA, who underwent placement of a magnetic catheter-based system under fluoroscopic guidance at six institutions. Daily chest radiographs were obtained until there was union of the magnets. Magnets were then removed and replaced with an oro- or nasogastric tube.

The average length of follow-up was 9.3 years (range 1.42-17.75). Eleven (85%) patients had type A, pure EA, and 2 (15%) had type C with previous fistula ligation. The average length of time to achieve anastomosis ranged between 3 to13 days. No anastomotic leaks occurred, and all the patients had an expected esophageal stenosis that required dilation given the 10F coupling surface of the magnets (average 9.8, range 3-22). Six patients (46%) had retrievable esophageal stents, and two underwent surgery; one of them had a perforation after dilation and thus underwent segmental resection and re-anastomosis; the other one had a recalcitrant stricture requiring resection and re-anastomosis; yet all maintained their native esophagus without interposition. Eleven (92%) were on full oral feeds at the time of follow-up.

The authors concluded that the use of magnets for treatment of long gap[5] EA is safe and feasible and accomplished good long-term outcomes. The main complication was esophageal stricture, although all patients maintained their native esophagus. A prospective observational study is currently enrolling patients to evaluate the safety and benefit of a catheter-based magnetic device for EA.

Greenstein J, Megan E, Tiernan K, Hageman JR, Zaritzky M (2018) Magnetic Anastomosis as a Minimally Invasive Treatment for Esophageal Atresia. NeoReviews, Vol 19, No. 9. DOI: 10.1542/neo.19-9-e533.

Summary

In this article, there is a review of what Flourish™ is and its indications, describing how the procedure is performed as well as the reported outcomes and potential complications of this approach. The authors included a description of a single case of a patient who underwent the procedure in whom magnetic coupling was observed almost immediately. In the early morning of post-procedure day 3, the patient developed signs of infection with fever, elevated white blood cell count, and elevated C-reactive protein level. Cultures did not grow a pathogen, but the infant was treated for 7 days with Vancomycin and Cefepime and showed clinical improvement.

[5] Long-gap EA, defined as cases in which a primary anastomosis of both ends of the esophagus cannot be performed without significant tension, is a technically challenging condition to treat. It is commonly measured during fluoroscopy and there is no standard distance defining it (Shieh HF, Jennings RW. Long-gap esophageal atresia. Semin Pediatr Surg 2017; 26:72-77., Baird R, Lal DR, Ricca RL, et al. Management of long gap esophageal atresia: A systematic review and evidence-based guidelines from the APSA Outcomes and Evidence Based Practice Committee. J Pediatr Surg 2019; 54:675-687).

Ten days after the procedure, the patient experienced a severe respiratory decompensation requiring sedation and pharmacologic paralysis.

Because of the infant's clinically unstable condition, magnet removal was delayed until post-procedure day 13; however, luminal continuity was noted on day 10 after magnet placement. For removal of the magnets under fluoroscopic guidance, a stiff guide wire was advanced into the esophageal magnet end. The retention balloon on the magnetic gastrostomy catheter was deflated and both magnets were then gently pushed down from the oral end until they exited the gastrostomy site on the skin surface. An orogastric tube was then left in place after the magnetic catheters were removed. The patient remained taking nothing by mouth for 2 weeks after magnet removal until reevaluation with an esophagram demonstrated anastomotic stenosis without evidence of a contrast leak.

Weekly esophageal dilating procedures were performed over four consecutive weeks to ensure an appropriate esophageal luminal diameter. The patient was subsequently transferred back to his home institution for ongoing intensive care.

The authors concluded that further investigation is necessary to explore the pathophysiology underlying the sepsis like response demonstrated in some patients after magnet placement, as well as the high rates of postprocedural esophageal stenosis.

Literature Review Conclusion

The literature review is one aspect of scientific data used in the overall continued surveillance of safety and probable benefit for HDE devices. Multiple factors influence the utility of the literature review including data limitations within the literature, such as non-specific data presentation that is not designed for evaluation of safety and probable benefit, along with, for some devices, limited numbers of relevant articles

For the current reporting period, only two articles were found including a total of 14 patients. The benefits noted in the reviewed literature outweigh the safety elements found. The average length of time to achieve anastomosis ranged between 3 to13 days among 13 patients included in one study. No anastomotic leaks occurred, and all 13 patients had an expected esophageal stenosis that required dilation. Six of the 13 patients had retrievable esophageal stents, and two underwent surgery; yet all maintained their native esophagus without interposition. The main complication was esophageal stricture, although all patients maintained their native esophagus. A single case report referred anastomosis achievement "almost immediately" but develop an infection that was treated with antibiotics. Ten days after the procedure, the patient experienced a severe respiratory decompensation requiring sedation and pharmacologic paralysis.

The current clinical evidence found in the literature is limited to 14 patients reported in two different articles. The findings in these publications are not different than those from the PAS. Due to the limited sales of the device, a possible explanation of the similarity of these findings is the inability to distinguish how many patients are participating in all three studies.

It is important to note that both articles have Dr. M. Zaritzky as senior author who, according to the articles' disclosure statement, is a medical consultant for Cook Medical, and shares the patent

and future royalties of Flourish™. We recommend continued monitoring of the literature for adverse events and probable benefits of the Flourish™ device in pediatric patients with esophageal atresia.

VIII. Overview of Medical Device Reporting

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 and FDA's internal MDR database 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.
- MDRs did not identify if patients were PAS patients and there is a possibility that MDRs may report on the same patients that were in the PAS.
- 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. To this end, there is a possibility that MDRs may report on the same patients that were in the PAS as MDRs did not identify if patients were PAS patients.
- MDR data is subjected 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 Flourish™ Pediatric Esophageal Atresia Device - H150003

MDR Search Methodology

In our 2019 update to the PAC, FDA found zero MDRs in the timeframe up to November 30, 2018. For this updated MDR analysis, the database was searched using the following search criteria:

A. Search 1
   - **Product Code:** PTK
   - **Report Entered:** between December 1, 2018 and May 31, 2020

B. Search 2
   - **Brand name:** FLOURISH%
   - **Report Entered**: between December 1, 2018 and May 31, 2020

C. Search 3
   - **Premarket submission number**: H150003
   - **Report Entered**: between December 1, 2018 and May 31, 2020

The searches resulted in identifying ten MDRs. All of the MDRs were submitted by the manufacturer. There were six out of ten MDRs reported on the same patients that were in the PAS.

The ten MDRs included six serious injury reports and four device malfunction reports. All MDRs are individually reviewed and discussed below. Table 4 below provides a highlight of the MDR analysis. Each column of the table is further discussed in the following sections.

TABLE 4: Overall Highlights of MDR Analysis

	Patient age (Months)	MDR event type category	Time to Event (TTEO) (Days)	Anastomose failure	Esophageal Leak	Fistula	Stenosis	Failure to advance	Patient device interaction problem	Off-label use	Reposition device due to anastomosis not formed	Explant device due to advance failure	Second Device Implanted	Surgery post anastomosis failure	Esophageal dilation due to anastomosis stricture
MDR1	3.5	Injury	10	Yes					Yes	Yes	Yes	Yes		Yes	
MDR2	2.6	Malfunction	13	Yes				Yes			Yes	Yes			
MDR3	Blank	Malfunction	13	Yes				Yes				Yes			
MDR4	2	Malfunction	9	Yes				Yes				Yes			
MDR5	4	Injury	6				Yes								Yes
MDR6	3.1	Injury	16	Yes				Yes				Yes		Yes	
MDR7	Blank	Injury	4	Yes	Yes			Yes				Yes		Yes	
MDR8	3.6	Injury	12				Yes		Yes						Yes
MDR9	Blank	Malfunction	14	Yes						Yes		Yes	Yes		
MDR10	Blank	Injury	6	Yes		Yes		Yes	Yes		Yes	Yes		Yes	
				Patient Problem Codes				**Device Problem Codes**			**Patient Re-intervention**				

Event Type by Patient Age

Table 4 above provides the distribution of the MDRs by reported event type and patient age. Six MDRs identified pediatric patient age from 2 to 4 months old, and the remaining four MDRs did not provide a specific patient age. These included six injury MDRs and four malfunction MDRs.

Time to Event Occurrence

An analysis of the Time to Event Occurrence (TTEO) was performed. The TTEO is based on the implant duration and was calculated as the time between the Date of Implant and the Date of Event. For those reports without a date of event, the TTEO was calculated using the reported date of implant removal. All ten MDRs reported the implant date and event date or explant date. The TTEO ranged from 4 days to 16 days with an average of 10 days (SD± 3.8 days). Please refer to Table 4 above for the TTEO information.

Characterizations of the 10 MDR Narratives of Pediatric Events from December 1, 2018 –May 31, 2020 as it relates to TTEO:

A. TTEO within the first 7 days of implant. (N= 3)

- A 4-month-old patient was reported by a physician regarding a stricture of the anastomosed site. The Flourish™ pediatric esophageal atresia device was placed with the patient under general anesthesia. The length of the esophageal gap was 1.0 cm. At completion of the procedure, the Flourish™ magnets were in the distal most portion of the esophageal ends. Four days post-placement of the Flourish™ device, an anastomosis was considered achieved with an esophagram showing connected flow of contrast agent between upper and lower esophageal ends. The Flourish™ device was removed six days post-placement. The patient underwent an esophageal dilation due to a stricture of the anastomosed site seven days post device removal. No other complications reported.

- An unknown age pediatric patient was reported by a physician regarding an esophageal pouch leak in the lower esophageal area. A Flourish™ pediatric esophageal atresia device was placed with the patient via an endoscopic procedure. Four days post-placement of the Flourish™ device, the physician injected contrast and found an esophageal leak in the lower esophageal pouch. The leak was in the same location as the lower magnet of the device. The Flourish™ device was removed the same day due to the detection of the esophageal leak. The esophageal leak was treated conservatively and requiring insertion of a chest tube. The patient was undergoing a surgery to repair the esophageal atresia.

- An unknown age pediatric patient was reported by a physician regarding a perforation identified by a contrast study. The Flourish™ pediatric esophageal atresia device was placed with the patient. After daily X-ray was performed, a misalignment of magnets was seen. A contrast study was done and identified a perforation near the distal magnet of the device. The surgeon took the patient to the operation room and found the leak was from an existing right main bronchus fistula. The fistula was never diagnosed before the use of Flourish™. The Surgeon surgically repaired the fistula and the esophageal atresia. The Flourish™ device was also removed at the same time, which was six days post-placement.

B. <u>TTEO between 8 days and ≤ 14 days of implant. (N=6)</u>

- A 2-month-old patient was reported by a physician regarding a failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device under general anesthesia. The length of the esophageal gap was slightly less than 4 cm. At completion of the procedure, distal esophageal segment was found to be short as viewed through the thoracotomy. The Flourish™ device was removed due to failure to achieve anastomosis nine days post-placement. A surgery to repair the atresia is planned.

- A 2.6-month-old patient was reported by a physician regarding failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device under general anesthesia. The length of the esophageal

gap was 2 cm. One of the magnets (oral catheter) was found to be loose before placing it in the patient. Another Flourish™ device was opened and the oral catheter from the second device was used to finish the case. The magnets were repositioned three times due to migration of ends of magnets further apart. The Flourish™ device was removed due to no progress made to achieve anastomosis thirteen days post-placement. The device was discarded. The patient has cardiac issues. Surgical repair is not planned at the time of this report, and additional attempts to achieve anastomosis with the Flourish™ device are under consideration.

- A 3.5-month-old patient was reported by a physician regarding failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device under general anesthesia. The length of the esophageal gap was measured at 3.9-4 cm. The physician had a difficult time placing the distal magnet due to the location of the original stoma and the patient anatomy. Once the Flourish™ device was in place, imaging was done to confirm the placement of the magnets. It was noted the gap was greater than 4 cm. The physician repositioned the magnets on the second day of the magnets being placed, and the gap appeared to be 3.2 cm after repositioning. The Flourish™ device was removed due to failure to achieve anastomosis ten days post-placement. The patient underwent thoracotomy to repair the esophageal atresia. The patient exited the study on the same day of surgery.

- An unknown age pediatric patient was reported by a physician regarding failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device. The length of the esophageal gap was 3.8-4 cm. There was no complication reported during the device placement procedure. The Flourish™ device was removed due to failure to achieve anastomosis thirteen days post-placement. It is unknown if the patient underwent surgery post-Flourish™ removal to repair the atretic gap.

- A 3.5-month-old patient was reported by a physician regarding an esophageal stenosis post anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device under general anesthesia. The length of the esophageal gap was measured at 2 cm. The Flourish™ device was removed after achieving anastomosis 12 days post-placement. The patient underwent an esophageal dilation of a stricture at the anastomotic site fourteen days following removal of the device.

- An unknown age pediatric patient was reported by a physician regarding failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device. The length of the esophageal gap was 4 cm but with tension applied. The Flourish™ device was removed due to failure to achieve anastomosis 14 days post-placement. The surgeon took the patient to an operation room and mobilized the esophagus and placed a second device, the magnets achieved anastomosis this time five days post placement.

C. TTEO between >14 days of implant. (N=1)

- A 3-month-old patient was reported by a physician regarding failure to achieve anastomosis. It was noted that the patient was placed with a Flourish™ pediatric esophageal atresia device under general anesthesia. The length of the esophageal gap was 3 cm. The magnets were repositioned multiple times during the two weeks post placement. The Flourish™ device was removed due to no progress made to achieve anastomosis 16 days post-placement. Surgical repair was scheduled at the time of this report.

Reported Patient Problem Codes (PPC)[6]

Table 4 above provides the reported patient problem codes found in the MDRs reviewed during this year's analysis, differentiated by patient age. The top reported patient problem code is "Anastomose failure" (n=8), followed by "Stenosis" (n=2), and "Esophageal leak" (n=1) and "Fistula" (n=1). The patient problem "Anastomose failure" is related to device failure to advance. Nine of the ten reports stated the device was not returned for evaluation.

Reported Device Problem Codes (DPC)[7]

Table 4 above provides the reported Device Problems for all MDRs differentiated by patient age. The top reported device problem code used in this analysis period is "Failure to advance" (n=6), followed by "Patient and device incompatibility" (n=2), and "Off-label use" (n=2).

A review of reports found that the device problem code "Failure to advance" was included as "Anastomosis failure." Repositioning of the device, device explant, or surgery were interventions used for the patients. The report of "Patient device incompatibility problem" is related to device off-label use (atretic gap was greater than indicated in the device labeling).

In one of the ten reports, the device was returned to the manufacturer for evaluation. The investigation could not determine the root cause because the actual use conditions could not be duplicated in the laboratory setting. Due to a variety of clinical conditions such as patient anatomy or progression of disease state, the manufacturer could not reproduce the actual conditions of product usage during their laboratory analysis, which limits their ability to conclusively determine a cause. The returned device met all specifications. Prior to distribution, all Flourish™ pediatric esophageal atresia devices are subjected to a visual inspection and functional testing

[6] The total PPC does not equal the total MDR count since one MDR might have multiple patient problems. Patient problem codes indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis.

[7] The total DPC does not equal the total MDR count since one MDR might have multiple patient problems. Device problem codes describe device failures or issues related to the device that are encountered during the event.

to ensure device integrity. A review of the device history record confirmed that the specific lot met all manufacturing requirements prior to shipment.

The clinical events for the ten pediatric MDRs found in this analysis involve complaints of anastomotic failure, which corresponding to the device issue of failure to advance. The noted interventions were surgical repair of atresia and explant of devices.

Re-Interventions in Pediatric Patients from 12/1/2018 through 5/31/2020

Re-interventions addressing types of clinical events reported above are listed in Table 4. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

Death Event

As stated above in Section VI, a PAS patient died 40 days post-procedure. In addition to esophageal atresia, the patient had a history of trisomy 21, low ears, duodenal atresia, ventricular septal defect, and patent ductus arteriosus. The cause of death was reported as "hypovolemic shock in setting of postnatal hydrops in setting of complicated trisomy 21 with EA." The patient had "worsening hypotension despite maximizing support and development of multi-system organ failure (including respiratory failure, oliguria and then anuria- kidney failure, GI failure)." The parents elected to compassionately discontinue ventilator support. The investigator reported the death as unrelated to the study device and study procedure. This information is outlined above in the PAS narrative.

This death was not submitted as an MDR. Per 21 CFR 803.3 manufacturers are required to report to the FDA within 30 days of learning that any of their devices may have caused or contributed to a death or serious injury. An MDR may be submitted in the future regarding this death.

Conclusions Based on MDR Review

- There are ten pediatric MDRs submitted for the Flourish^{TM} Therapy System between December 1, 2018 and May 31, 2020.
- The Time to Event Occurrence (TTEO) was calculated for five MDRs based on the available information contained in the reports. The TTEO ranged from 4 days to 16 days, with an average of 10 days (SD± 3.8 days).
- The most frequently reported patient problem was anastomosis failure, and the most frequently reported device problem was device failure to advance.
- The manufacturer's evaluations of the device issues were hindered due to devices not being returned in most cases (9 out of 10 MDRs).
- As noted earlier,there were six out of ten MDRs reported on the same patients that were in the PAS .
- The MDRs discussed above are consistent with the lower rate of successful anastomosis seen in the PAS and non-PAS patients post approval.

IX. SUMMARY

The data evaluated for the HDE of Flourish™ supported the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use, and the device was granted approval. Esophageal anastomosis was achieved in all of the described cases, both as first line, as well as second line therapy. The probable benefits of earlier anastomotic repair and fewer surgical complications outweighed the risks of higher rate of anastomotic strictures requiring balloon dilation and/or esophageal stenting in the appropriate patient. This was coupled with thorough labeling, favorable input from experts in the field with the majority favoring device use, and an acceptable training program and post-approval study in place.

There are differences seen in the post-market clinical data that are difficult to interpret. Of the twenty total patients treated with the device since the device approval, in only half (50%, 10/20) of these patients was anastomosis achieved. Measuring technique may account for some of these differences. Other reasons may include scarring of the esophageal ends from previous intervention, age of the patient, site where the procedure was performed, atresia type, and/or physician experience. However, the limited data does not allow for definitive conclusions.

There is inadequate information regarding post-procedure stricture rate post device approval as there were limited patients treated in the PAS study that achieved an anastomosis (2/6). Of the three patients in the PAS in whom anastomosis was achieved, two developed stricture requiring balloon dilation. Overall there is inadequate information for comparison of post procedure stricture rates between patients who received the Flourish™ device as compared to patients that underwent surgical repair.

The literature review provided valuable information about long-term outcomes following use of the Flourish™ device. As discussed above, stricture formation is a long-term complication as 13 of 13 treated patients had an expected stricture that in some cases required esophageal stenting (n=6) or surgery (n=2). However, a majority (n=11) of patients were ultimately tolerating full oral feeds and maintained their native esophagus without interposition grafting therefore suggesting that patients benefited from using Flourish™.

Even with the postmarket clinical data, FDA still finds it reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury when used as indicated in accordance with the directions for use. Our analysis considers the probable risks and benefits of currently available devices or alternative forms of treatment; with the Flourish™ device, anastomotic repair can occur earlier than a thoracotomy and avoids several surgical complications. This is especially important for a condition that is usually co-existent with other potentially serious comorbidities. In these cases, potential benefit of device use to provide a less invasive approach and avoid a major surgical procedure would outweigh the risks.

Cook notified FDA in May of 2020 of their intent to modify the PAS study to increase enrollment and meet the requirement of providing safety and effectiveness data for a minimum of twenty patients. FDA is currently interactively working with Cook to explore modifications of

the PAS study in order to meet the PAS objectives. As part of a revised PAS study plan, more frequent PAS reporting may be required.

Based on the available data, and considering the probable benefits and risks, FDA concludes that the HDE remains appropriately approved for pediatric use. FDA will continue routine surveillance including MDR and literature reviews. FDA will provide focused updated safety and use data to the PAC in 2021.

Therefore, FDA recommends continued surveillance of the Flourish™ device. FDA will report the following to the PAC in 2021:

- Annual distribution number
- Literature review
- MDR review
- Revised PAS study and follow-up results