FDA Executive Summary

Prepared for the
Fall 2021 Meeting of
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 of the Humanitarian Device Exemption (HDE) device, Flourish™, since the 2020 Pediatric Advisory Committee (PAC) update. The current reporting period is June 1, 2020 through April 30, 2021. 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.

In our September 2020 update to the PAC, FDA reported on the observed decreased effectiveness of the device, relative to the data used to approve the HDE. In this update, we will be reporting on a small number of serious adverse events associated with the use of the Flourish device, the proposed mitigations, and next steps.

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.

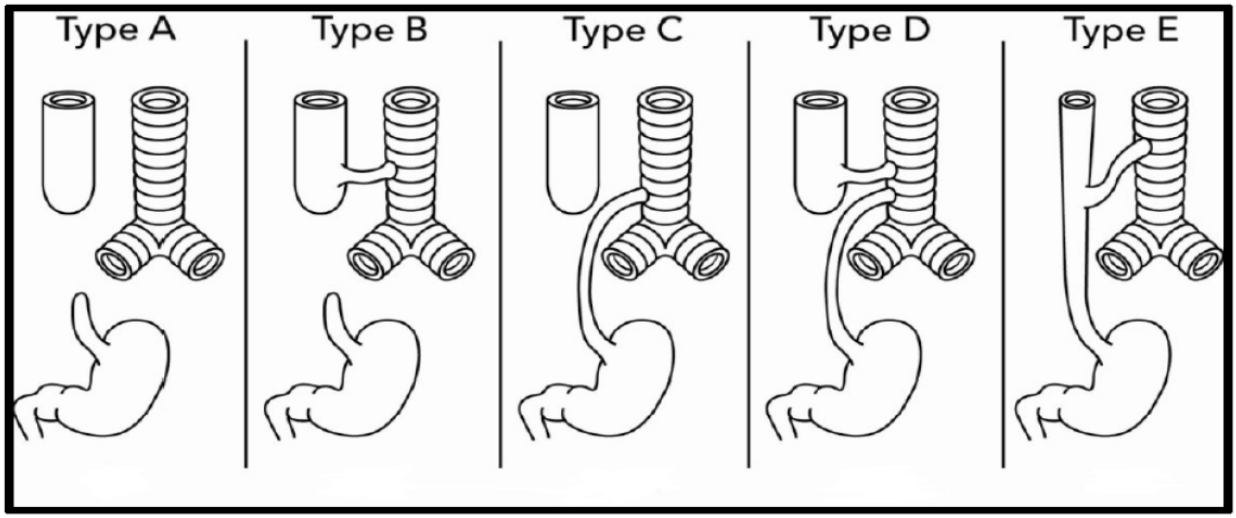

Figure 1: Types of Atresia

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.

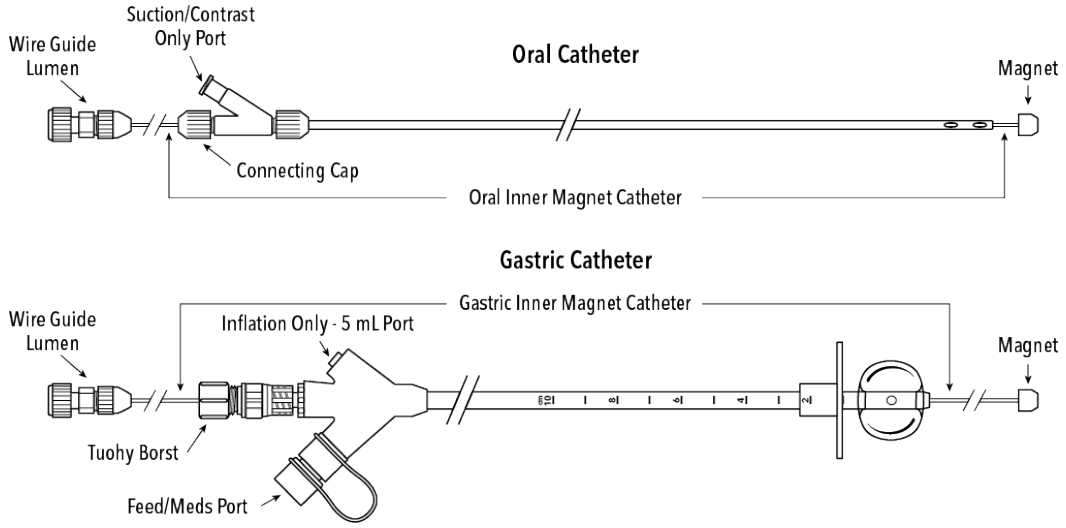

Figure 2. Flourish Pediatric Esophageal Atresia Anastomosis Device

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).

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.

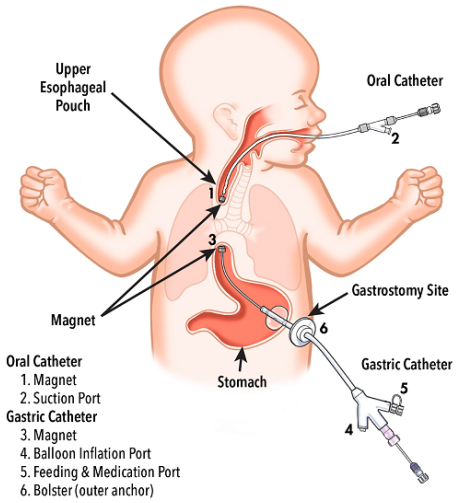

Figure 3. Device Illustration

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:

Table 1. Regulatory History

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 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 gap measurment	October 25, 2019

PAS changed from a prospective study to a real-world evidence (RWE) design which allows both retrospective and prospective data collection from medical records	October 2, 2020
HDE Supplement to implement labeling change to enhance safety during device placement and indwelling period.	December 10, 2020

HDE Clinical Data (Pre-market)

As we previously reported in the 2020 update to the PAC, 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, although the patient was swallowing oral secretions well, four months after device placement the patient had persistent stenosis. This was 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.

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[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.

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 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 was concluded that 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.

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.

The sponsor states that 34 devices were sold/shipped during the reporting period, well below the 8,000 device ADN requirement. Typically, two devices are shipped for each potential case and return is requested for devices that are not used. The 34 devices sold includes those that were returned to the Sponsor unused. During the previous 2020 PAC, the sponsor reported 33 devices sold during the prior reporting period.

The table below provides the number of devices sold and used during the current reporting period of June 1, 2020 to April 30, 2021.

Table 2. Device Use During Reporting Period

Reporting Period	Total Sales	Total Implanted	Patients Not in Post Approval Study (Non-PAS)	Patients in Post Approval Study (PAS)
June 1, 2020 to April 30, 2021	34	9 *	9	0

*Of the 9 devices implanted, 3 patients were treated outside the U.S. (Canada).

VI. MEDICAL DEVICE REPORTING

Serious adverse events were reported between June 1, 2020 and May 31, 2021, and are described in more detail below. Following these adverse events and upon FDA inquiry, Cook enacted additional labeling changes and communications to address these adverse events. Please see Section VII of this memo for additional detail on those labeling changes. FDA chose to expand the reporting period for MDRs from April to May 2021 to present the PAC with a serious adverse event that was received in May (Tracheoesophageal Fistuala); the clinical usage for that adverse event occurred prior to May 2021.

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.
- 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.
- Three of the MDRs in this reporting period were submitted as many as five to six months late after the firm became aware of the information; the clinical usage in these three reports occurred during the reporting period for the 2020 PAC update (reporting period through May 2020).

MDRs Associated with Flourish™ Pediatric Esophageal Atresia Device - H150003

MDR Search Methodology

For this updated MDR analysis, the database was searched using the following search criteria:

A. Search 1
   - **Product Code:** PTK
   - **Report Entered:** between June 1, 2020 and May 31, 2021

B. Search 2
   - **Brand name:** FLOURISH
   - **Report Entered**: between June 1, 2020 and May 31, 2021

C. Search 3
   - **Premarket submission number**: H150003
   - **Report Entered**: between June 1, 2020 and May 31, 2021

The searches identified eight MDRs. Seven of the MDRs were submitted by the manufacturer, and one MDR was submitted voluntarily.

One MDR was a duplicate submitted from different reporting sources (manufacturer and voluntary) regarding the same event. In the narrative below, the duplicate MDRs are presented as a single MDR. The seven MDRs included 0 death, six serious injuries, and one device malfunction report. None of the seven MDRs reported patients that were in the post-approval study.

All MDRs are individually reviewed and discussed below. Table 3 below provides a highlight of the MDR analysis. Each column of the table is further discussed in the following sections.

TABLE 3: Overall Highlights of MDR Analysis

	Patient Age (Months)	MDR Event Type	Time to Event (TTEO) (Days)	Anastomose Failure	Esophageal Perforation	Tracheoesophageal Fistula	Stenosis	Failure to Advance	Positioning Failure	Surgery	Reposition Device due to anastomosis not formed	Explant Device due to device advance failure	Second Device implanted	Esophageal Dilation due to anastomosis stricture
MDR1	<12	Injury	4	Yes				Yes		Yes		Yes		
MDR2	<12	Injury	13	Yes				Yes		Yes		Yes		
MDR3	6	Injury	8	Yes				Yes		Yes		Yes		
MDR4	7	Injury	35		Yes*		Yes							Yes
MDR5	<12	Injury	4	Yes	Yes					Yes		Yes		
MDR6	8	Malfunction	0	Yes				Yes	Yes	Yes	Yes			
MDR7	4.4	Injury	14			Yes				Yes	Yes		Yes	
						Patient Problem Codes		Device Problem Codes			Patient Re-intervention			

Note: *unconfirmed perforation

Event Type by Patient Age

Table 3 above provides the distribution of the MDRs by reported event type and patient age. Four MDRs identified a pediatric patient age from 4 months to 8 months; three MDRs identified a pediatric patient as under one year of age respectively but did not provide a specific patient age.

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 seven MDRs reported the implant date and event date or explant date. The TTEO ranged from 0 day (same day) to 35 days with an average of 11 days (SD± 10.8 days). Please refer to Table 3 above for the TTEO information.

Characterizations of the Seven MDR Narratives of Pediatric Events from June 1, 2020 –May 31, 2021 as it relates to TTEO:

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

- MDR 1 An under one-year 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 around 4 cm. The device was left in place for four days and the magnets did not move or attract. The Flourish device was removed due to failure to achieve anastomosis. The patient stayed hospitalized for a surgical approach to repair the atresia.

- MDR 5 An under one-year old pediatric patient was reported by a physician regarding an esophageal perforation in the lower esophageal area. A Flourish pediatric esophageal atresia device was placed with the patient. Magnets were repositioned post-operation in radiology as the distal magnet seemed to have fallen out of place. The gap was reduced to 2.2 cm by day 3. However, on day 4, the patient started to have a fever. Imaging showed that the distal magnet had a deviated trajectory, having moved cephalic and lateral, to the patient's right. Contrast study showed some drainage back into the stomach, however, it also showed contrast draining and collecting into the right bronchus, likely indicating perforation of distal pouch. This prompted the physician to remove both magnets without further incident. A chest tube was placed, and a small amount of fluid was drained. A thoracotomy will be performed next for further assessment and treatment. The root cause for perforation has not been identified.

- MDR 6 An 8-month-old pediatric patient was reported by a physician regarding a Flourish pediatric esophageal atresia device placement failure. The physician took the patient to the operating room and tried to place the Flourish magnets but was not successful. It was reported that the distal esophagus was very thin and short, and the magnet placed kept sliding out. Per the user, the gap distance was within the range of indication for use but could not approximate the upper and lower pouches less than 2 cm without some tension. The procedure was aborted. The healthcare facility tested the magnets ex vivo and found that they did not connect until they were about 1.5-1.7 cm apart, just as observed during the aborted clinical procedure.

The device was not returned to the manufacturer for evaluation. The manufacturer tested a device from the same lot and found that the magnets showed attraction towards each other when within 4 cm of each other but do not fully pull together at this distance. This is the expected behavior of the device per the manufacturer. Prior to distribution, all Flourish pediatric esophageal atresia devices are subjected to a visual inspection and functional testing to ensure device integrity. A review of the device history record confirmed that the lot said to be involved met all manufacturing requirements prior to shipment.

B. TTEO between 8 days and ≤ 14 days of implant. (N=3)

- MDR 2 An under one-year-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. The device was left in place for 13 days and the magnets did

not move or attract. The Flourish device was removed due to failure to achieve anastomosis on day 13 post placement. The patient stayed hospitalized for a surgical approach to repair the atresia.

- MDR 3 A 6-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. The upper magnet was introduced into the upper esophageal pouch. The lower magnet was introduced through the established existing stoma and placed in the most distal end of the esophageal pouch. The device was left in place for eight days and the magnets did not move or attract. The Flourish device was removed due to failure to achieve anastomosis on day eight post placement. The patient stayed hospitalized for a surgical approach to repair the atresia.

- MDR 7 A 4.4-month-old patient was reported by a physician regarding a life-threatening tracheoesophageal fistula after use of the Flourish device. A Flourish pediatric esophageal atresia device was placed in the patient and x-ray confirmed good placement. The surgeon and an interventional radiologist decided to leave a wire guide in the inner catheter of the lower Flourish catheter to be used for support. The manufacturer representative mentioned to the physician that the wire guide that was left in place could add friction and weight to the inner catheter. The magnet catheter was repositioned daily and replaced on day seven. On day nine, the physician applied force to the magnets to try to get them to come together and achieved anastomosis that same day. The manufacturer representative advised that the tension could cause a perforation. On day 14, the esophagram looked good and there were no leaks, the device was removed that day.

  Four days after the device removal, the patient started experiencing respiratory issues. The patient was tested positive for enterovirus/rhinovirus, and a surgical consult indicated a concern for the presence of a tracheoesophageal fistula. The patient was transferred to a sister hospital. A large tracheoesophageal fistula from the esophagus to the left main bronchus was confirmed by a bronchoscopy and an esophagoscopy. The patient’s condition decompensated and required an emergent surgery of thoracotomy. The patient’s medical history showed that the patient was born with a pure esophageal atresia.

  The manufacturer investigation concluded that the mostly likely root cause of the reported events was related to the use of the device. Specifically, the user applied force to the device to try and get the magnets to come together. The instructions for use include the following warning: "do not apply any force besides the magnetic pull onto the esophageal pouches to approximate them as this may result in perforation". Additionally, the user left the wire guide in place although the instructions for use state "remove pre-positioned wire guide...".

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

- MDR 4 A 7-month-old pediatric patient was reported by a physician regarding a potential esophageal perforation. It was noted that the patient was placed with a Flourish pediatric esophageal atresia device. At the time of the procedure, the gap length appeared to be 4 cm. The patient went to the neonatal intensive care unit (NICU) after the device placement. Per the instructions for use, the device's inner catheters should be in the unlocked position. The surgeon decided to leave the inner catheters in the locked position while pushing in on the inner catheters causing the magnets to come closer together, because when the inner catheters were unlocked, the magnets would regress back, and the gap length would be farther away. In one occasion, the magnets regressed back to 5 cm.

  On day 21 of the device placement, the surgeon notified the Cook representative that the magnets were touching. The surgeon did mention that they had left the inner catheters locked throughout the treatment and he would put tension on the catheters before locking them to approximate the esophageal ends. The surgeon further stated that magnets would not have come together without the pushing and locking of the device. The Cook representative mentioned this is the first time anyone had left the magnets in longer than 13 days. It was also mentioned that this was the first time that the method of putting tension on the inner catheters and locking had ever been done before. The physician also mentioned that he introduced the feeding tube into the lower esophageal pouch for more support of the lower magnet.

  One week after the magnets were touched, the physician sent to the Cook representative some images of the patient's esophagram, which indicated the magnets had likely perforated through the esophageal pouches [images indicated there is a gap with no contrast between the pouch and magnet]. The patient was taken to the operation room and the magnets were removed traditionally and a nasal jejunal tube was placed. The physician decided to do an endoscopy on the patient because the contrast did not move through the anastomosis area and to confirm if there was a perforation. The physician did dilate the anastomosis area under fluoroscopy. He did not see a leak; however, he was not able to get a direct visual. It could not be confirmed if a perforation occurred. The patient was sent home and was not symptomatic.

  The manufacturer investigation concluded that a product evaluation was not performed in response to this report because the product said to be involved was not provided to Cook for evaluation. The customer provided pictures of a contrast study done on the patient. Five pictures were included in the report; the magnets are shown to have come together. A potential perforation cannot be confirmed by the images provided. The device history record for the lot number said to be involved was reviewed. A discrepancy or anomaly was not observed with the product that was released for distribution.

Reported Patient Problem Codes (PPC)[5]

Table 3 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

[5] 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.

code is “Anastomose failure” (n=5), followed by “Esophageal perforation” (n=2), and “Stenosis” (n=1) and “Fistula” (n=1). The patient problem “Anastomose failure” is related to device failure to advance.

Reported Device Problem Codes (DPC)[6]

Table 3 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=4), followed by “Positioning failure” (n=1). 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. All reports stated the device was not returned for evaluation.

Re-Interventions in Pediatric Patients from 6/1/2020 through 5/31/2021

Re-interventions addressing types of clinical events reported above are listed in Table 3. This table summarizes the re-interventions identified in the narratives and the causal events leading to these re-interventions.

Conclusions Based on MDR Review

- There are seven pediatric MDRs submitted for the Flourish Pediatric Esophageal Atresia Device between June 1, 2020 and May 31, 2021.
- The Time to Event Occurrence (TTEO) was calculated for seven MDRs based on the available information contained in the reports. The TTEO ranged from 0 day to 35 days, with an average of 11 days (SD± 10.8 days).
- The most frequently reported patient problem was anastomosis failure, and the most frequently reported device problem was device failure to advance.
- There were two new serious adverse events, esophageal perforation (2), and tracheoesophageal fistula (1). In two of the three reports for serious adverse events, there was reported manipulation of the device that was inconsistent with the instructions for use, in an apparent attempt to support the magnet placement or bring the magnets closer together during the indwelling period. There was also one device placement failure due to the reported insufficient Flourish magnet attraction strength.
- The manufacturer’s evaluations of the device issues were hindered due to devices not being returned in all seven MDRs.

[6] 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.

VII. DEVICE UPDATES AND COMMUNICATIONS

In response to FDA's requests for information regarding the serious adverse events described in the MDRs, Cook has made labeling changes and is collecting additional information to address and reduce the risk of these adverse events. These mitigation strategies are described below.

A. Esophageal Perforation

Based on the perforation MDR reports received, FDA issued an additional information (AI) letter to Cook Endoscopy. FDA requested root cause and risk analysis for these perforation cases as well as their mitigation strategies in the AI letter. Cook responded that the root causes of perforation were identified as user-technique related, operational-context related, and possibly clinical-conditions related, respectively.

To mitigate future occurrences of modified technique use, Cook submitted a supplement for labeling revisions (H150003/S006). The labeling changes to the Instructions for Use and the physician PowerPoint training presentation were approved on December 10, 2020 and included the following:

- Providing enhanced recommendations for potential complications during the device indwelling period, including perforation/leak of one or both esophageal pouches or anastomotic site, which could result in additional procedures and/or death;
- Adding two warnings related to improper placement of the feeding tube into the lower esophageal pouch and applying force onto the esophageal pouches to approximate them; and
- Clarifying the locking status of the oral and gastric catheters during indwell.

B. Tracheoesophageal Fistula (TEF) and Magnet Attraction Strength

Based on the Tracheoesophageal Fistula MDR report received in MDR 7, and Magnet Attraction Strength not effective report received in MDR 6, FDA issued an AI letter to Cook Endoscopy. FDA requested root cause and risk analysis for the tracheoesophageal fistula and magnet attraction strength cases, results of evaluation/validation of device design meeting user needs as well as their mitigation strategies in the AI letter.

Cook responded to FDA's AI letter as follows::

a) A definitive root cause for the TEF adverse event (MDR 7) was not identified. Per the MDR, the esophagogram looked good upon Flourish removal with no apparent leaks; however, TEF was identified 4 days after Flourish removal. It is possible that the Flourish device could cause an acquired TEF (a TEF formed after device usage/procedure). Extensive pushing and locking of the magnets during the placement procedure (rather than letting the magnets make a progressive attraction) could predispose a patient to a perforation.

Cook identified the most likely root cause if the Flourish caused or contributed to the TEF to be abnormal use of the device by the user (the pushing and locking of the magnets for a long time during the placement procedure). Cook and FDA are engaged in discussions regarding labeling revisions, and Cook intends to submit a separate HDE Supplement for the labeling change.

b) Regarding the insufficient magnet strength, Cook stated that the force with which the magnets are pulling towards each other increases exponentially as the distance between them is reduced. *Ex vivo*, the magnets will appear to have little attraction force between approximately 1.5 cm and 4 cm of separation distance. This intrinsic characteristic of the magnets is beneficial, as the lower force allows the esophageal pouches to stretch towards each other over time to mitigate the risk of perforation. *In vivo*, there are multiple variables that can impact the effectiveness with which the magnets are able to move towards each other, including: scarring of the esophageal pouches or tethering of the esophageal pouches to adjacent structures via connective tissues.

   A device from the same lot as the device used in MDR 6 was tested along the length of a ruler and demonstrated that the magnets show attraction towards each other and some movement when within the 4 cm mark, but do not fully pull together at this distance. This is the expected behavior of the device. The test the physician performed "*ex vivo*", (as described in MDR 6), is consistent with the performance of a conforming device. The device history record for this specific lot of devices was reviewed and no discrepancies or anomalies were observed with released products.

   The ability to create an esophageal anastomosis with the Flourish device is related to the strength of the mating magnets. To maintain safe use, Cook noted that the device must not provide an excessive magnetic compression pressure such that the tissue between the magnets necroses before an adequate fusion of the esophageal pouches can be achieved, which may lead to anastomotic leaks. A literature review by Lambe et al. (2014)[7] quantified the magnetic pressure required to successfully achieve gastrointestinal and bilioenteric anastomosis from porcine survival models. Results showed that an ideal compression pressure should not exceed 60 N/cm^2 (at a 2 mm intermagnet space). An analysis was completed to characterize the compressive force of the magnets of the Flourish device at a 2 mm intermagnet space. Based on the forces recorded and the surface area of the mating surfaces of the magnets, a resulting compression pressure was calculated. The Flourish device exerts an average compression pressure of approximately 45.7 N/cm2 (range, 36.0 – 52.1 N/cm^2).

   Cook identified patient factors that could potentially impact effectiveness of magnet attraction and subsequent anastomosis, such as patient anatomy and fibrous tissue from prior surgeries. Variables may include the size of infant, length of esophageal pouches, location of PEG placement, and angle of the stoma to the lower esophageal pouch, and esophageal pouch orientation (esophageal pouch to the right or left of the spine), as well as fibrous tissue from prior surgeries in the vicinity of the atretic gap. However, currently,

[7] Lambe T, Ó Ríordáin MG, Cahill RA, et al. Magnetic compression in gastrointestinal and bilioenteric anastomosis: how much force? *Surg Innov*. 2014;21(1):65-73.

there are limited data available to assess any potential impact of these variables to the positioning of the magnets and the ability to achieve successful anastomosis. Cook does not provide strategies for device placement beyond the IFU and physician training PowerPoint, and given the reports of successful anastomosis in at least half of patients, Cook does not believe that a design change to alter the magnetic properties of the Flourish device is warranted at this time.

C. Product Return

From 6/1/2020 to 5/31/2021, none of the Flourish devices involved with the MDRs were returned to Cook for evaluation. An AI letter was issued to find out the cause for devices not being returned and to understand the efforts Cook made in collecting used devices for analysis. FDA requested Cook to provide a plan for facilitating user return of used devices to facilitate device evaluation and identification of root causes. Cook responded that they would encourage user facilities to keep devices that are involved in complaints and/or adverse events, and the physician training PowerPoint is being updated to proactively communicate to users the importance of returning used devices to facilitate device evaluations.

Conclusions

The serious adverse events prompted questions regarding user manipulation of the catheters and/or magnets. It is possible the manipulation of the device beyond the instructions specified in the labeling is due to lack of alignment of pouch ends during placement, even when the magnets are within 4 cm of each other. FDA is working with Cook to identify root causes and appropriate mitigations. The panel will be asked to comment on proposed mitigations, and the FDA expects to present more information regarding mitigation strategies at a future PAC meeting.

VIII. POSTMARKET CLINICAL DATA

In this section, we first provide a brief update on the nine patients implanted with the Flourish device during this reporting period, followed by an update on the work that has been done to help ensure future data collection in the post approval study (PAS).

Non-PAS Patients

In this reporting period, as of April 30, 2021 there were nine patients treated with the Flourish device; none were enrolled in the PAS study. Limited information is available on those patients. Cook reported that six of the nine patients achieved anastomosis. All nine patients were reported to have a pre-procedure atretic gap equal to or less than 4 cm; no relationship between atretic gap size and anastomosis success was observed. Information about stricture formation was unavailable. Information regarding the type of esophageal atresia was available for four out of nine patients; due to the limited information, no conclusions can be drawn regarding a relationship between anastomotic success and type of esophageal atresia. Some of the nine patients treated within this reporting period have been described in the MDR section above.

Table 4: Overview of non-PAS enrolled outcomes

Patients (in chronological order)	Non-PAS?	Pre-procedure gap measurement	Anastomosis Achieved?	Type of Esophageal Atresia
1	Yes	4 cm	Yes	Unknown
2	Yes	3 cm	Yes	A
3	Yes	1 cm	Yes	C
4	Yes	2.5 cm	No	A
5	Yes	1.0 cm	No	Unknown
6	Yes	2.3 cm	No	Unknown
7	Yes	2.2 cm	Yes	Unknown
8	Yes	2.4 cm	Yes	A
9	Yes	<1cm	Yes	Unknown

PAS Study Status

FDA's approval of the Flourish HDE was based on limited clinical data on device safety and probable benefit as well as a post-procedure stricture rate that was higher than that of standard of care surgical repair. As such, the Flourish device was approved on May 12, 2017 with a requirement to conduct a PAS as a condition of approval. The PAS study protocol, which was approved on April 27, 2018, describes the study as follows:

- 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 endpoints: Stricture at the anastomotic site leading to the need for intervention; peri-anastomotic leaks; and adverse events that are 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.

A total of 6 PAS patients were treated under this protocol and data on all 6 patients were previously presented to the PAC in 2019 and 2020.

Since the start of this PAS, the sponsor had difficulty enrolling patients into this study. To help ensure timely completion of a PAS that would collect useful clinical data to inform continued benefit-risk assessments in the postmarket space, FDA worked with the sponsor to revise the PAS from a purely prospective design to a hybrid prospective and retrospective study design. The revised PAS protocol, which was approved on October 2, 2020, differs from the original PAS in that it allows enrollment of patients who have already been treated, with a combination of retrospective and prospective real-world data collection from medical records. The revised PAS will also include 6 patients who were enrolled in the original PAS. A comparison of key study design elements between the original and revised PASs are presented below in Table 5.

Table 5. Comparison of original and revised PAS study designs

	Original PAS	**Revised PAS**
Approval Date	April 2018	October 2020
Study Design	Single-arm, observational study	
Patient Enrollment	Before Flourish treatment	Before or After Flourish treatment
Data Collection	Prospective data collection	Prospective and retrospective RWD collection from medical records
Number of Sites	15 Sites (at least 1 in the US)	
Number of Subjects	20 Patients	
Length of Follow-up	2 Years	
Primary Endpoints	Stricture at anastomotic site; peri-anastomotic leaks; and adverse events that are possibly, probably, or causally related to the device or procedure	
Secondary Endpoint	Successful anastomosis formation	
Study Status	Study closed on Oct 2020; 6 patients were enrolled	Expected study completion in Dec 2022; currently 0 new patients enrolled

During the current reporting period, no patients were enrolled in the PAS. Although there is no clinical data to present from the PAS this year, the sponsor has been laying the groundwork to establish the revised PAS at clinical sites. The sponsor is currently contacting healthcare providers to get their help in consenting patients who were treated with Flourish outside of the PAS since device approval; to date, there are 25 such patients. The revised PAS is expected to

be completed in December 31, 2022, with 2-year follow-up data on 20 patients who were treated with Flourish. At the next PAC meeting in fall of 2022, FDA expects to present more data from the near-completed revised PAS study.

IX. SYSTEMATIC LITERATURE REVIEW

Systematic Literature Review on the Safety and Probable Benefits 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.

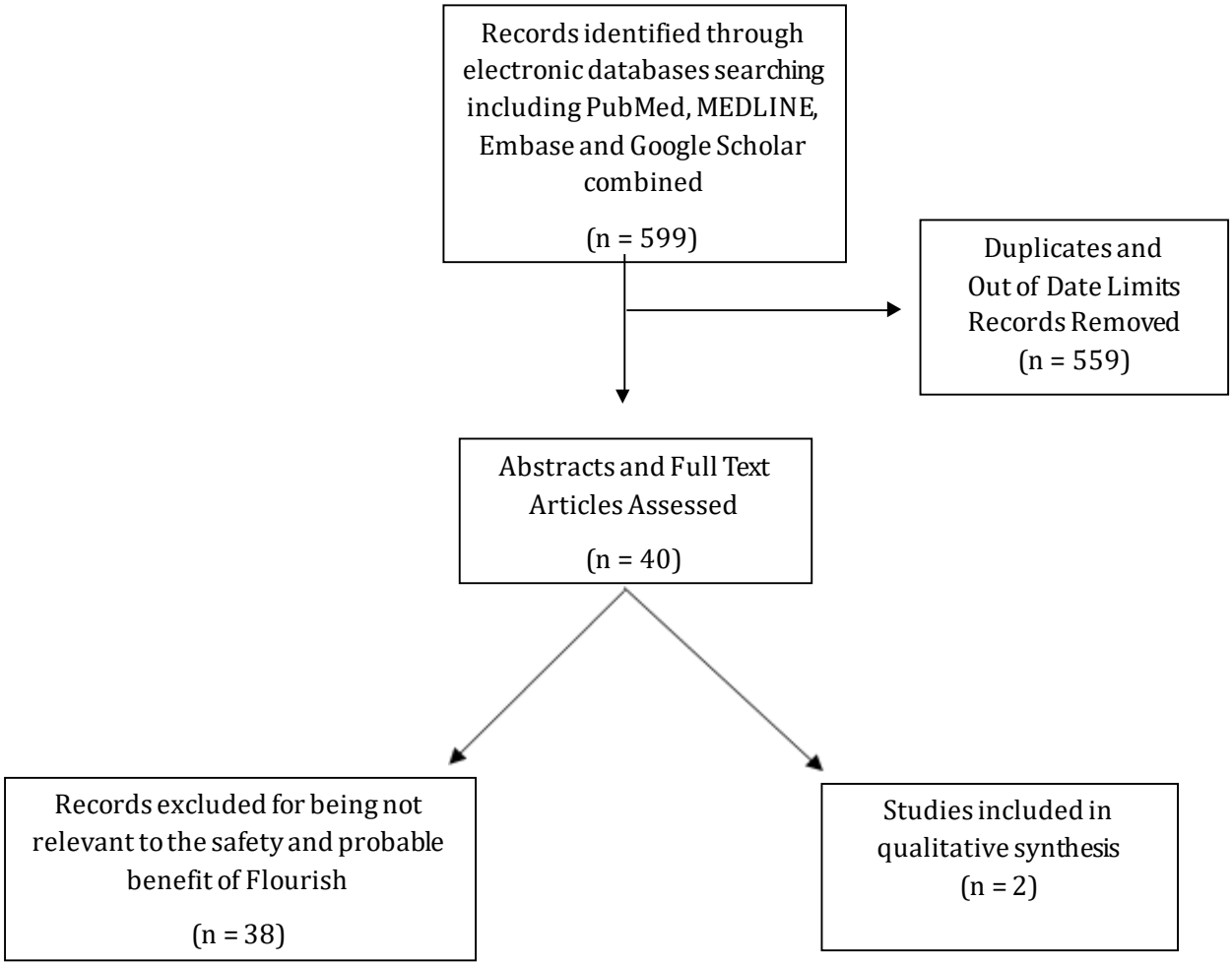
Methods
On June 4, 2021, a search was conducted using the PubMed, Embase and Google Scholar databases with the following search terms and strategies:

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

The current search was restricted to articles published between June 1, 2020 and April 30, 2021 including clinical studies in humans, pediatric use, and written in English. Only publications including clinical research studies, systematic literature reviews, and meta-analysis were considered for pertinence. 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 599 articles from PubMed, MEDLINE, Embase and Google Scholar combined. After filtering by the date limits and excluding duplicates, 559 articles were excluded and 40 remained for full text article review. After full texts were reviewed, all but two articles 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. The summaries of the two pertinent articles are included below.

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



Wolfe E, Zidane M, Hancock BJ, Lum Min SA, Zaritzky M, Keijzer R (2020) Magnamosis for esophageal atresia is associated with anastomotic strictures requiring an increased number of dilatations. Journal of Pediatric Surgery. Elsevier Inc. Science Direct. Volume 55, Issue 5, Pages 821-823. https://doi.org/10.1016/j.jpedsurg.2020.01.022

Summary

Background/Objective

Magnamosis is a novel technique which utilizes high power magnets to anastomose the esophageal ends in children with esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF), theoretically avoiding the need for thoracotomy. Techniques to repair long gap EA include delayed primary anastomosis, esophageal myotomy, tension-induced lengthening, or esophageal replacement via gastric transposition, colonic interposition, or jejunal interposition. Preservation of the native esophagus is ideal; however, the creation of anastomosis under tension can lead to increased risk of anastomotic leak, stricture, and gastroesophageal reflux. The objective of this study was to compare anastomotic stricture formation requiring dilatation after Magnamosis versus after conventional anastomosis.

Methods

This is a retrospective study. According to the authors, their center (Children's Hospital Research Institute of Manitoba, University of Manitoba, Canada) treated the first 3 cases of EA ± TEF with Magnamosis in Canada. However, when Magnamosis was attempted in one of the three patients, Magnamosis was unsuccessful as the ends were misaligned and the proximal pouch did not move. Therefore, this patient was excluded from the study. The patient study population was derived from the Winnipeg Surgical Database of Outcomes and Management (WiSDOM). The WiSDOM database contains demographic and management information for all children born with any of eight surgical congenital anomalies treated in Winnipeg between 1991 and 2015. The number of post-intervention dilatations was compared to controls from the WiSDOM database, which includes all children with EA ± TEF treated between 1991 and 2015. The controls had EA ± TEF treated with pouch-to-end anastomosis or colonic interposition ($n = 65$). Mann–Whitney U tests were used with $p < 0.05$ being significant.

Results

Authors were able to follow the patients for up to 9 months. The 2 Magnamosis cases had a mean of 13.5 dilatations, compared to 2.6 for the controls ($p = 0.022$) managed with pouch-to-end anastomosis or colonic interposition having a mean of 2.3 and 2.7 dilatations respectively (Table 1 below).

Table 1
Number of postintervention dilatations compared between the magnamosis cases and controls, as well as compared between the magnamosis cases and those managed with pouch-to-end anastomosis or colonic interposition.

	Magnamosis ($n = 2$)	Controls ($n = 65$) Pouch-to-end ($n = 57$) Colonic interposition ($n = 8$)	P-value
Dilatations (mean ± sd)	13.5 ± 2.1	2.6 ± 4.1	0.022*
		2.3 ± 6.0	0.021*
		2.7 ± 3.9	0.106

The two patients successfully treated with Magnamosis were described as follows: Case A is a female born at 34 weeks' gestation who was diagnosed antenatally with Tetralogy of Fallot, and postnatally with a long gap EA with a distal TEF. Her fistula was ligated at birth, and she had primary repair at 5 months of age. Following continuity, she developed a severe stricture, and her continuity was able to be reestablished using Magnamosis. Case B is a male born at 36 weeks' gestation who was diagnosed antenatally with an isolated EA. Thoracotomy for primary repair failed and the ends were aligned for Magnamosis. The magnets were connected after 24 hours and anastomosis was established after 5 days.

Conclusion

The results indicate that Magnamosis was successful in two out of three patients. In those that was successful, it was found associated with more post-intervention dilatations than conventional anastomotic techniques, suggesting that Magnamosis results in more frequent and/or more resilient anastomotic strictures.

Disclosure Statement

Dr. M. Zaritsky is a Medical adviser for Cook Medical and shares the patent and future royalties of Flourish. All the other authors have no conflicts of interest to declare.

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(2020) Magnetic compression for anastomosis in treating an infant born with long-gap oesophageal atresia. A case report. Medicine (2020) 99:42.
http://dx.doi.org/10.1097/MD.0000000000022472

Summary

Background and Objective:
Neonatal long-gap esophageal atresia (LGEA) with tracheoesophageal fistula (TEF) is an uncommon but serious congenital malformation of the esophagus in newborns, and it remains challenging for pediatric surgeons. Magnetic compress has been shown to be effective for the treatment of LGEA in children and adults. However, the implementation of this unique technique for neonatal LGEA has not been evaluated. This is a case report of a female infant born at 37 weeks of gestation.

Methods:
Prenatal ultrasound imaging revealed signs of esophageal atresia, including the absence of the gastric bubble and polyhydramnios. A diagnosis of LGEA with TEF was confirmed at birth by contrast X-ray. She was treated with magnetic compression anastomosis (MCA) following an esophago-esophagostomy. Two magnetic rings were customized, and the MCA was conducted during the same stage surgery of ligating the TEF.

Results:
Under the magnetic force, the 2 magnet rings pulled along the gastric tube to achieve anastomosis. The magnet placement was successful, as determined when the patient was observed postoperatively in the neonatal intensive care unit. Anastomotic leakage occurred at 7 days, while healing was achieved on day 25. Magnet removal was performed at 36 days post-operation, and the esophagram demonstrated the absence of perforations or other early complications. After magnet removal enteral nutrition was continued via a gastric tube for 4 weeks at post-operation. The upper gastrointestinal contrast confirmed the anastomotic patency perfectly after 3 months. The patient was followed up for 18 months and exhibited durable esophageal patency without dysphagia.

Conclusion:
The study describes a case of LGEA with TEF type IIIa in an infant, which was successfully treated with one surgical procedure for esophago-esophagostomy, which achieved magnetic compression anastomosis (MCA) by thoracotomy and endoscopy. The newborn patient was confirmed to have LGEA with an approximately 3 cm gap. Notably, anastomosis was achieved on day 36, exceeding the previously reported in the literature mean time of 4.2 to 6.0 days. These results suggest that MCA is feasible and effective for treating LGEA in infants.

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: one article was published by Wolfe et al 2020 including 3 patients, that, although it is not mentioned, their Magnamosis treatment was most likely carried out using Flourish. Anastomosis was achieved in two of the patients. The other article was published by Liu SQ et al 2020 using customized ring magnets instead of Flourish.

Wolfe et al. 2020 results indicate that Magnamosis is associated with more post-intervention dilatations than conventional anastomotic techniques. Even when the results were statistically significant using the Mann-Whitney test, the authors only had 2 patients treated with Magnamosis compared to 65 controls. Therefore, the evidence is not clinically robust. Additionally, the authors included the mean and standard deviation in Table 1 while the Mann-Whitney test compares mean ranks. It does not compare means using standard deviations. In any case, this article results suggest that Magnamosis results in more frequent and/or more resilient anastomotic strictures.

Liu SQ et al. 2020 describes a single case of long-gap (3.0 cm) esophageal atresia with tracheoesophageal fistula type IIIa in an infant, which was successfully treated with one surgical procedure for esophago-esophagostomy, achieving magnetic compression anastomosis on day 36 by thoracotomy and endoscopy.

The current clinical evidence found in the literature is limited to 4 patients reported in two different articles. The safety findings in these publications are not different than the previously known safety information at the time of HDE approval. Wolfe et al. 2020 compared patients treated with different procedures and found that Magnamosis is associated with more frequent anastomotic strictures than the comparators. The article by Liu SQ et al. 2020 describes a magnetic compression successfully achieving anastomosis using two customized magnetic rings similar but not the same as Flourish.

It is important to note that Dr. M. Zaritzky is a co-author in the Wolfe et al. 2020 study, and was a senior author in two articles included last year in the "PAC Executive Summary" 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.

X. SUMMARY

The Flourish device was approved with limited clinical data that supported a reasonable assurance of safety and probable benefit when used in accordance with the indications for use. In the premarket data from literature and compassionate/emergency use cases, 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 a PAS requirement.

During the current reporting period, only 9 patients were treated with Flourish. Post-market data in these 9 patients show an evolving benefit-risk profile relative to when device was approved. Specifically, successful anastomosis formation was observed in 6 of 9 patients in the 2021 reporting period and 10 of 20 patients in the 2020 reporting period, compared to 16 of 16 patients in the premarket data.

There were a number of safety issues including perforations, TEF, stricture formation, and insufficient magnet strength leading to lower occurrence of anastomosis formation. It should be noted that, because all 9 patients were treated outside of the PAS, safety outcomes in these patients are largely incomplete. Therefore, it is difficult to draw any definitive conclusions based on these insufficient data. The root causes for adverse events has not been identified for all events; however, infrequent Flourish usage may be an impediment to physician proficiency with the procedure, which can impact patient outcomes. Additionally, physician lack of adherence to the instruction for use, such as locking status of oral and gastric catheters and excessive manipulation of the catheters to approximate the magnets may contribute to complications such as perforation, leaks, or stricture formation. The reasons for lack of adherence to the instructions for use may be related to functionality of the device in specific clinical scenarios, and will be explored and clarified with the device sponsor. Additional safeguards will be considered as appropriate.

We expect to have a clearer picture of the device's benefit-risk profile with completion of the PAS and continued evaluation of patients who are treated outside of the post-approval study. Given that the revised PAS is expected to be completed by the end of 2022, FDA plans to present findings from a near-complete PAS with 2-year follow-up in 20 patients to the PAC in fall of 2022.

The literature review provided supporting information about longer-term outcomes following Flourish treatment in 4 patients. Three of the 4 patients achieved successful anastomosis; however, all 3 patients developed stricture formation that required dilation. Ultimately, all 3 patients tolerated full oral feeds, suggesting that patients benefitted from Flourish treatment.

Even with the limited postmarket 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 potential surgical complications. This is especially important for a condition that is usually co-existent with other potentially serious comorbidities. In these cases, probable benefit of device use to provide a less invasive approach and avoid a major surgical procedure would outweigh the risks. However, given the serious adverse events observed in this reporting period, FDA and Cook are discussing potential labeling and training revisions to reduce the risk of these adverse events.

FDA recommends continued surveillance of the Flourish device. FDA will report the following to the PAC in 2022:

- Annual distribution number
- PAS follow-up results
- MDR review
- Literature review
- Any additional device/labeling changes or manufacturer communications