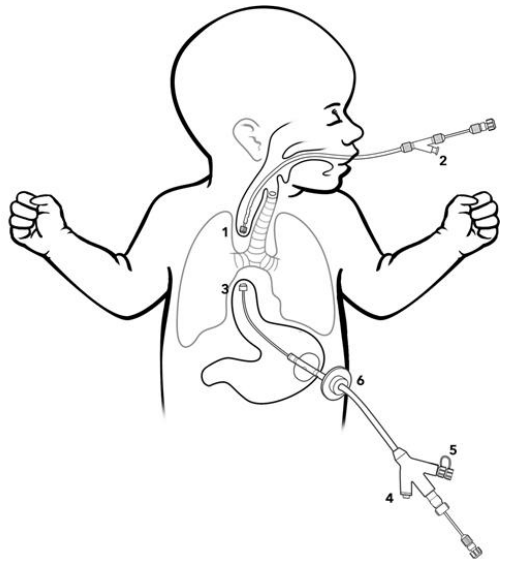
Flourish® Pediatric Esophageal Atresia Device



Sponsor Presentation to the Pediatric Advisory Committee

17Sep2021

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Agenda

- Brief company overview, commitment to unmet needs
  - Ted Heise, PhD, RAC, VP Regulatory & Clinical, MED Institute, Inc.
- Clinical need, impact of open surgery, and expected benefit of Flourish device use
  - Mario Zaritzky, MD, University of Chicago School of Medicine, Comer Children's Hospital
  - Bethany Slater, MD, University of Chicago School of Medicine, Comer Children's Hospital
- High level summary of post-approval experience
- Implemented and proposed labeling changes
- Post-approval study (PAS) updates

Overview of Cook Medical

- Founded in 1963, Cook Medical is a family owned, multinational medical device manufacturer with world headquarters in Bloomington, Indiana.
- Our company employs over 12,000 employees worldwide, 8,000 of which are employed in North America.
- We manufacture over 10,000 different products and innovate minimally invasive diagnostic and therapeutic products for treatment of a wide variety of diseases.

Long-term Commitment to Pediatric Patients

- Cook helped craft the enabling legislation for HDEs; and contributed to the implementing regulation
- Pioneered first HDE approval (Harrison Fetal Bladder Stent)
- Provided comments on all amendments of HDE regulations
- Submitted an accepted NEST project to evaluate collecting Real World Data (RWD) in support of a pediatric device approval
- Actively pursuing additional small-market pediatric products (e.g., within HBD for Children program)
- Approval of the Flourish Atresia Device—a minimally invasive option for select infants that avoids need for major surgery

Humanitarian Device

Authorized by federal law for use in the treatment of 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. The effectiveness of this use has not been demonstrated.

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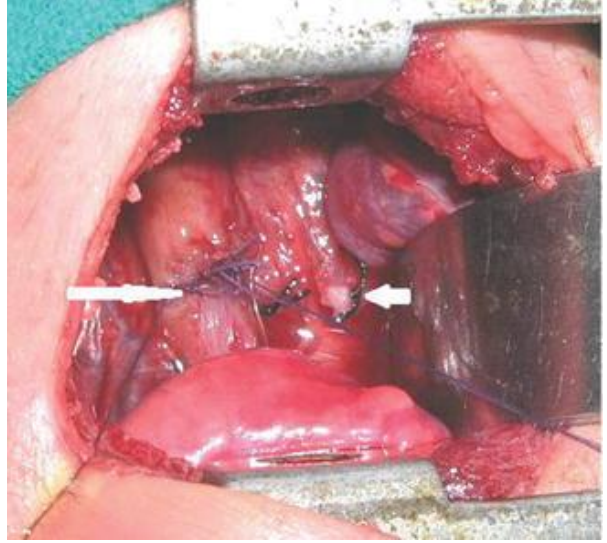
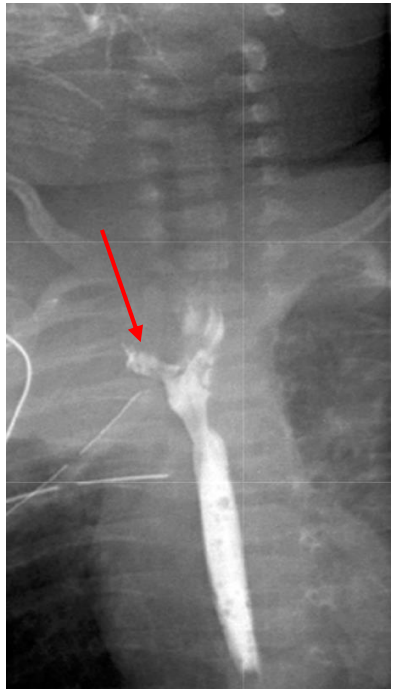
Complications of Surgical Repair

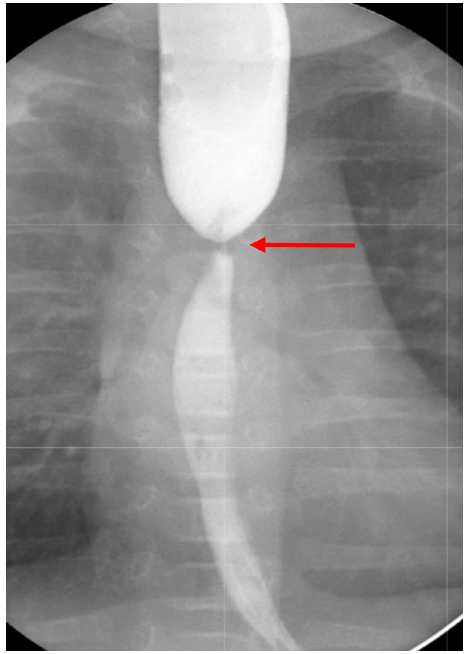
Repair of EA with or without TEF

- Anastomotic leak – 13-16%
- Stricture – 11% up to 80%
  - Need for repeated balloon dilatation not uncommon
- Recurrent fistula – 3-14%
- Long-term:
  - Gastroesophageal reflux
  - Tracheomalacia
  - Quality-of-life issues





Leak



Stricture

Congenital Anomalies of the Esophagus, In Pediatric Surgery, ed: Coran, et al. 7th edition

Complications of Surgical Repair (Types A&B)

Table 3
Postoperative complications to the different surgical approaches.

Surgery related complications[a]	Total ($n = 326$)	DPA ($n = 223$)	GPU ($n = 27$)	GT ($n = 26$)	CI ($n = 25$)	JI ($n = 1$)	Other[e] ($n = 24$)	*p*- value
Anastomotic leakage, *n (%)*	74 (22.7%)	50 (22.4%)	7 (25.9%)	7 (26.9%)	2 (8.0%)	0	8 (33.3%)	0.491
Anastomotic stricture, *n (%)*	175 (53.7%)	138 (61.9%)	8 (29.6%)	13 (50.0%)	2 (8.0%)	0	14 (58.3%)	<0.001
GER, *n (%)*	105	91	1	0	4	-	9	<0.001
Total number of thoracotomies, *mean ± SD*	1.1 ± 1.1 ($n = 125$)	1.4 ± 1.3 ($n = 77$)	0.1 ± 0.3 ($n = 15$)	1 ± 0 ($n = 7$)	0.3 ± 0.5 ($n = 6$)	0 ($n = 1$)	0.9 ± 0.6 ($n = 19$)	<0.001
Mortality[d], *n (%)*	15 (4.6%)	9 (4.0%)	1 (3.7%)	2 (7.7%)	3 (12.0%)	0	0	<0.001

A systematic review of 10 years through 2016 showed:

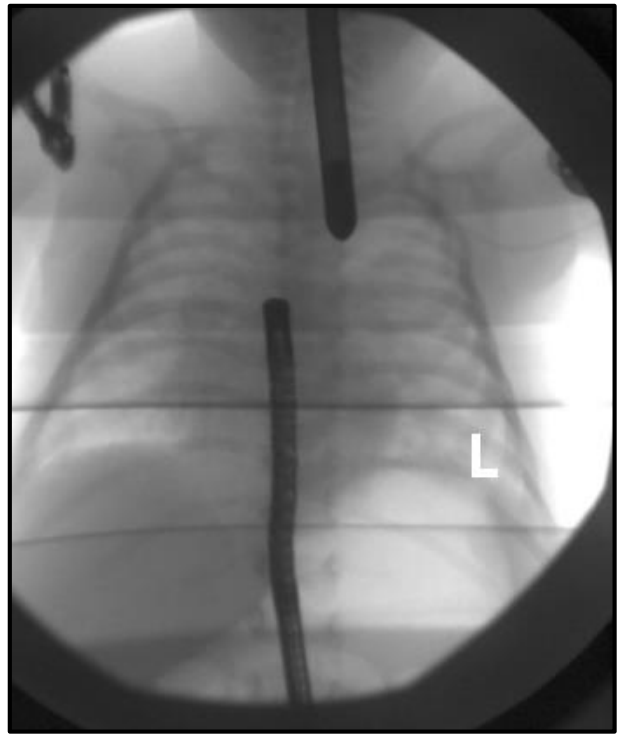
- Mortality rate of nearly 5%
- Additional surgery required in 8.6% of cases

[a]There are missing values. [b]Other complications were mainly pneumothorax, fistulation, infection and ischemia. [c]Fundoplication due to GER: Nissen fundoplication ($n = 41$), Thal fundoplication ($n = 3$) and Toupet fundoplication ($n = 3$). [d]Mortality within the first postoperative year. [e]Other interventions that were applied are listed in Table 1. A – in the table indicates no reporting of the specific issue.

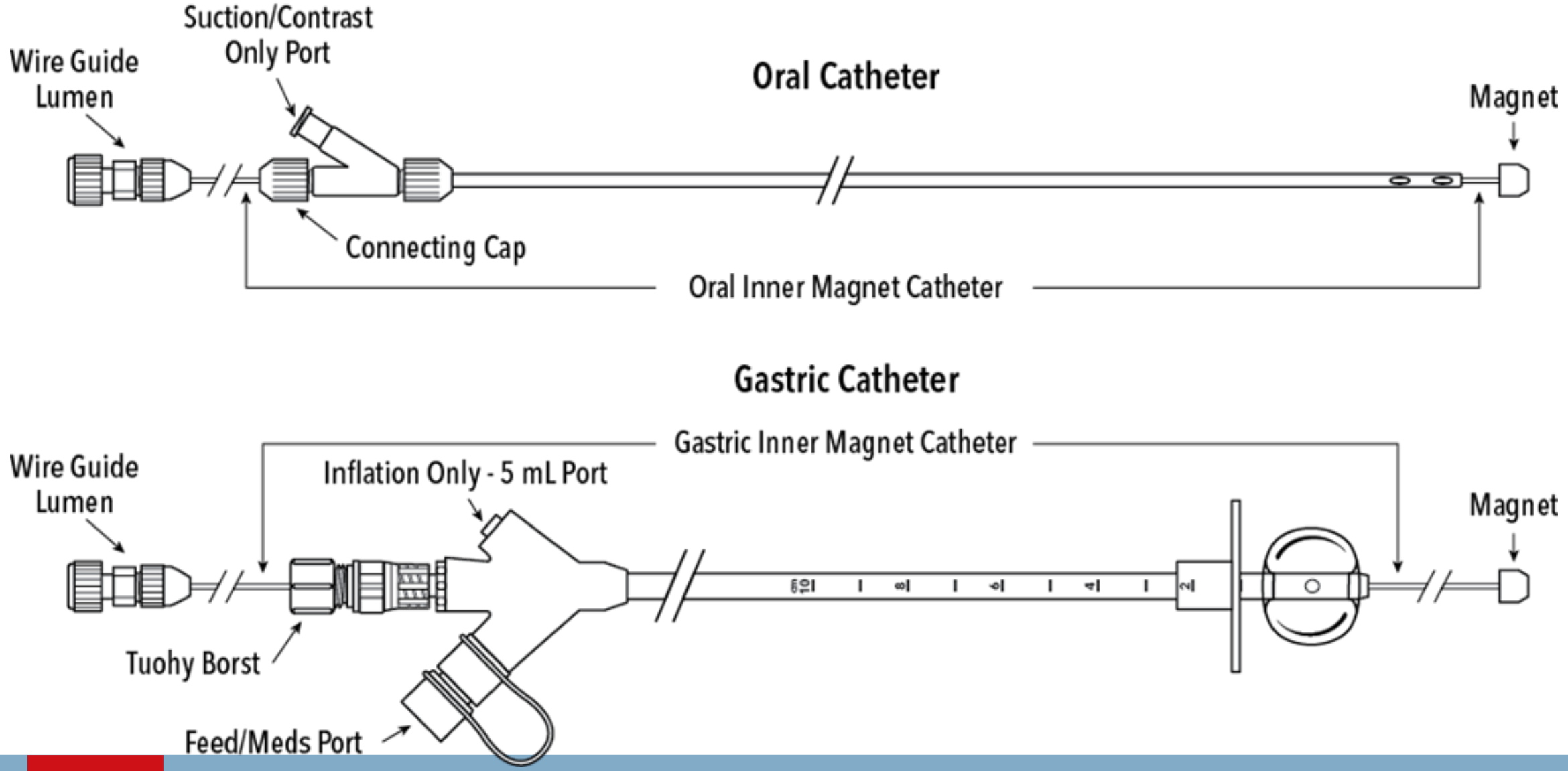
Stadil, T. Koivusalo, A. Svensson, JF. Jönsson, L. Lilja, HE. Thorup, JM. Sæter, T. Stenström, P. Qvist, N. Surgical treatment and major complications within the first year of life in newborns with long-gap esophageal atresia gross type A and B – a systematic review. *J Pediatric Surg*. 2019;54:2242-2249.

Long-gap Operative Management – Technically Challenging

- Variety of techniques used
- Multiple operations
- Repeated anesthetics
- Prolonged operative times
- Significant physiologic stress to patient



Flourish Pediatric Esophageal Atresia Device



Expected Benefits of Flourish (Nonsurgical alternative for esophageal anastomosis)

- Avoid an invasive surgical procedure
- Avoid dissection on esophageal pouches
  - Potential for decreased dysmotility of esophagus
  - Decrease risk of injury to recurrent laryngeal nerve
  - No need for Azygos vein ligation, which prevents rare potential for hemorrhagic events
- May be particularly beneficial for patients with cardiac or other anomalies

Overview of Post-Approval Experience

- Used in 33 infants from May 2017 through July 2021
  - Includes one compassionate use case prior to distribution
  - 3 patients have had two devices used
- Device has been used in 8 patients in 4 hospitals in Canada under Special Access provisions
- Device has been used in 25 patients in 16 hospitals in the U.S.
- The primary safety outcome (major adverse events)[a] and secondary endpoint for evaluation of probable benefit (successful anastomosis)[b] are known for all 33 patients

[a] Stricture at the anastomotic site leading to the need for intervention; peri-anastomotic leaks; and other adverse events and/or complications potentially related to the device or procedure (including, but not limited to: GERD, tracheomalacia, esophageal dysmotility, and/or recurrent asthma or pulmonary infections)

[b] 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

Total Post-Approval Experience: Outcomes

Reporting Period		Cases (% of total)	Success (% of cases)	Adverse Device Effects[a]
2018 – 2019	PAS	4 (57%)	1 (25%)	0[b]
	U.S.	2	1 (50%)	0
	Can	1	1 (100%)	0
	Total	**7**	**3 (43%)**	0
2019 – May 2020	PAS	2 (14%)	1 (50%)	0
	U.S.	8	5 (62%)	0
	Can	4	2 (50%)	1[c]
	Total	**14**	**8 (57%)**	**1**
Jun 2020 – May 2021	PAS	0 (0%)	N/A	0
	U.S.	6	5 (83%)	2[d]
	Can	3	1 (33%)	1[e]
	Total	**9**	**6 (67%)**	**3**
2018 – May 2021 Totals	PAS	6 (20%)	2 (33%)	0
	U.S.	16	11 (69%)	2[d]
	Can	8	4 (50%)	2[c,e]
	Total	**31[f]**	**18 (58%)**	**4 (13%)**

[a] Dilation of post-anastomotic strictures not included
[b] Subsequent death due to pre-existing underlying comorbidities (no MDR considered necessary)
[c] Esophageal pouch leak (MDR 1037905-2020-00115); unrecognized pre-existing TEF (MDR 1037905-2020-00187)
[d] Potential perforation (MDR 1037905-2020-00334); TEF (MDR 1037905-2021-00194)
[e] Perforation (MDR 1037905-2020-00407)
[f] Includes one compassionate use case prior to reporting periods and commercialization of approved device

Considerations for Successful Anastomosis

- There are likely factors that influence success (e.g., prior thoracic surgery, patient anatomy, connective tissue tethering of pouches to adjacent structures)
    - More complete data to come from the PAS may be helpful in better understanding factors that affect success

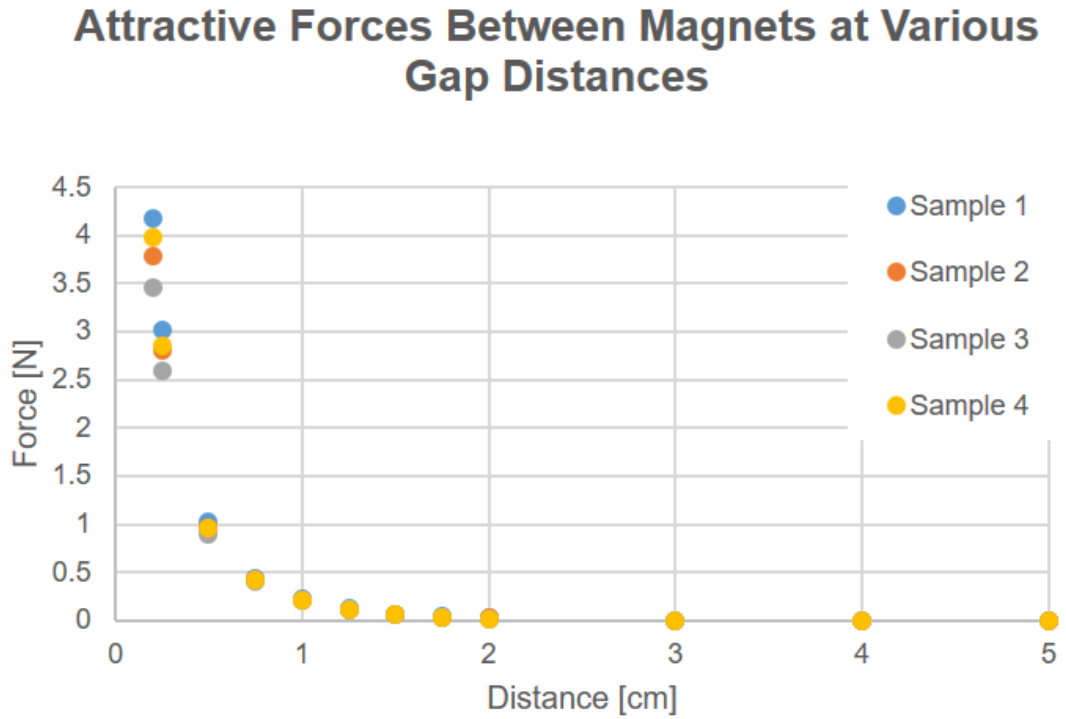
Importantly, infants without successful anastomosis remain surgical candidates (device use does not limit subsequent surgery)

A complaint[a] regarding magnet forces and questions from FDA prompted review of the magnet forces

[a] MDR 1037905-2021-00096

Considerations for Magnet Forces

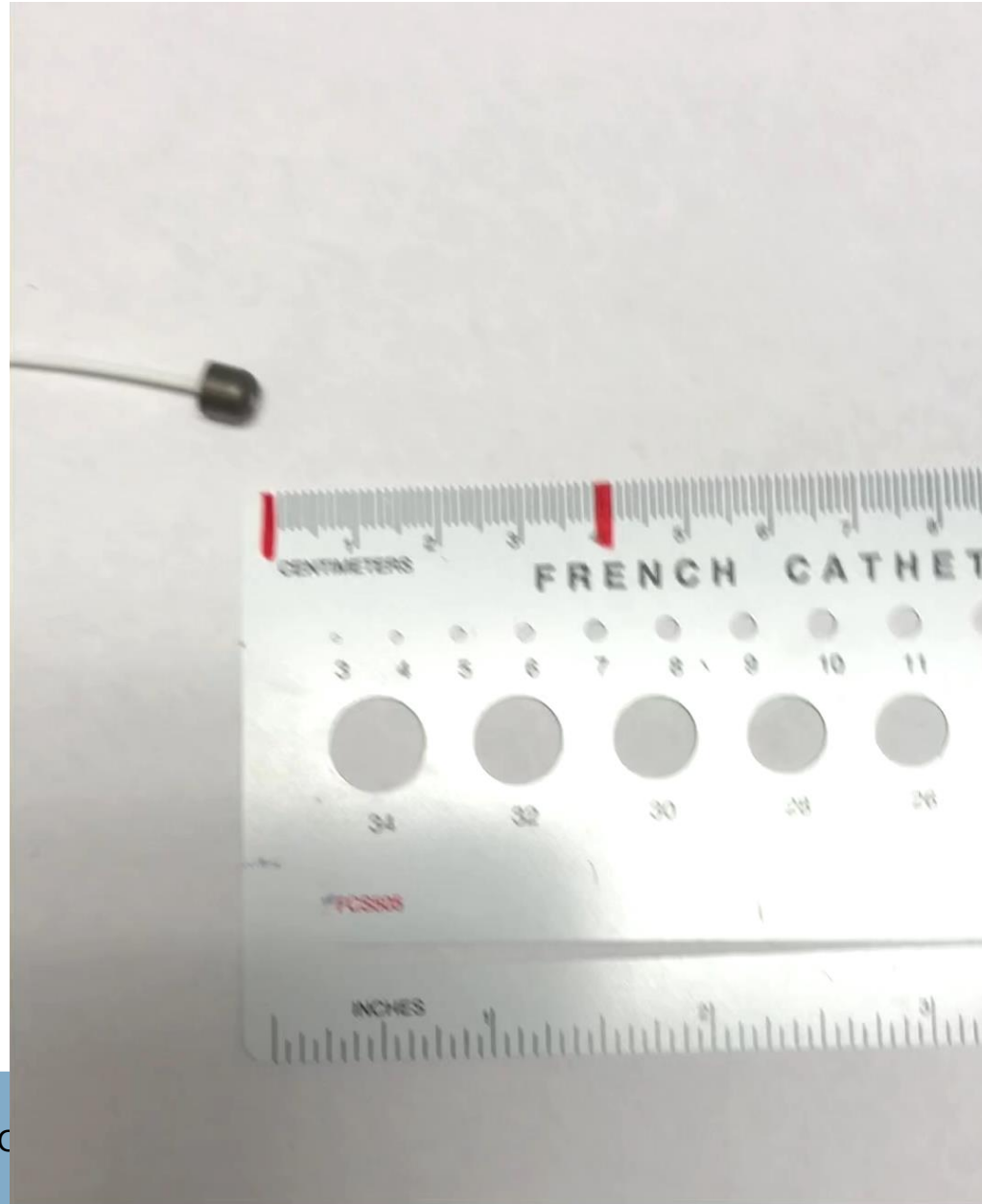
- "*Compression pressure [at a distance of 2 mm] should not exceed 60 N/cm²*" [1]
  - Higher compressive pressure may increase risk of perforation and/or anastomotic leaks
- For the Flourish surface area (0.104 cm²) the force at 2 mm should be < 6.2 N
- Upper 99% confidence limit of measured Flourish magnet force at 2 mm is 4.8 N
  - Provides a reasonable safety margin
  - Force decreases exponentially with separation
- A meaningful increase in force at 4 cm separation would cause a potentially unsafe increase at 2 mm (i.e., >> 6 N)



[1] Lambe T., et al. Magnetic compression in gastrointestinal and bilioenteric anastomosis: How much force? (2014) Surgical Innovation, 21 (1), pp. 65-73.

Attractive Forces at Greater Distances

- *Ex vivo*, the magnets visibly attract each other at distances greater than 4 cm. This confirms the magnetic fields are interacting
- Factors that could impact magnetic attraction:
  - Alignment of magnets
  - Proximity to metallic objects
- Importantly, in clinical use:
  - This same magnet design formed an esophageal anastomosis in the premarket patients[2]
  - Successful anastomoses have been achieved in infants with gap lengths up to 4 cm



[2] Zaritzky M., Ben R., Johnston K. Magnetic gastrointestinal anastomosis in pediatric patients (2014) Journal of Pediatric Surgery, 49 (7) pp. 1131-1137.

Post-approval Clinical Experience: Safety

- 4 MDRs filed in 2020 and 2021 related to esophageal pouch leak,[a] potential perforation,[b] perforation,[c] or possible perforation with tracheoesophageal fistula (TEF)[d]
  - In every case, the physician exceeded recommended device use by modifying device placement and maintenance (e.g., leaving G-tube advanced into lower esophageal pouch, applying added force/tension to the magnet catheters, locking the magnets)
  - It is unclear whether the TEF was an unappreciated pre-existing defect

[a] MDR 1037905-2020-00115 (filed in prior PAC reporting period)

[b] MDR 1037905-2020-00334

[c] MDR 1037905-2020-00407

[d] MDR 1037905-2021-00194

Implemented Labeling Changes to IFU and Training Materials

- Changes to address potential esophageal leak/perforation and strengthen warnings against abnormal use were approved by FDA on December 10, 2020
  - Expanded the list of potential complications during device indwell to include perforation/leak of one or both esophageal pouches or anastomotic site, which could result in additional procedures and/or death
  - Added warnings to not advance and maintain the G-tube into the lower esophageal pouch and to not apply force onto the catheters to approximate them
  - Clarified the locking status of the oral and gastric catheters during indwell

IFU Changes Proposed to FDA

- Cook has proposed to FDA additional labeling changes intended to further enhance safety, including:
  - Addition of new TEF as a potential complication
  - Additions to warnings to clarify that applying sustained force to the catheters in an attempt to advance the magnets may increase the risk of perforation or TEF
  - Clarifications to language regarding repositioning the magnets during indwell

Summary of Post-Approval Experience

- The rate of successful anastomosis has increased from 43% → 57%→ 67% year over year
  - Suggests that changes in labeling have improved case selection
- The device is safe when used as recommended:
  - Balloon dilatation, though not uncommon, is also often necessary for infants whose EA has been treated surgically
  - Several cases of esophageal leak or perforation were associated with use of device well outside of recommendations; none occurred when labeling was followed (vs. 13-16% rate following surgery)
  - No unanticipated adverse device effects
  - No patient deaths (vs. published 5% rate with surgery)
- Importantly, infants without successful anastomosis remain candidates for surgery—device use does not limit options.
- We conclude that the benefit:risk ratio remains favorable

Condition of Approval Study (PAS)

- Required to collect additional data from 20 patients by December 31, 2022 for a final report due on March 31, 2023
- Patients were initially enrolled under a traditional, investigative study design
  - Enrollment challenges prompted a change to a more pragmatic study design
- The study was changed to a RWD collection
  - October 02, 2020: FDA approved the revised study plan
  - December 28, 2020: a Central IRB approved the revised study plan
  - February – April 2021: local IRBs at 5 hospitals approved the revised study plan

PAS Progress

- 9 patients in the U.S. are included
  - 6 patients were enrolled under the traditional, investigative study design
  - 3 patients were enrolled under the RWD study design (all since end of 2021 reporting period)
  - This represents 45% of the required total of 20
- 7 patients have met a study exit point and 2 patients remain active study participants
- PAS progress should accelerate now that many HCPs have been contacted to participate and understand the new approach

Projected Cases for PAS Data Collection

Hospital Location	Number of Potential Patients	Outstanding Prerequisite
US	1	Parental informed consent
US	1	Hospital research staff training
US	2	Parental informed consent or a waiver of consent
US	1	Local IRB approval
US	1	Budget and contract
US	1	Budget and contract
Canada (*n= 4*)	8	Submission of Investigational Testing Authorization (ITA) and study approval by Health Canada[a]

[a] The Flourish device is not commercially available in Canada and has been used under Special Access provisions

- With the 9 cases already collected, we expect these cases will bring our total to the required 20
- The additional case data will inform improvements in future case selection and labeling

Summary and Conclusions

- The Flourish device provides an important minimally invasive treatment option for appropriate infants, often avoiding the need for major surgery
- Clinical experience to date has been largely favorable
  - Rate of successful anastomosis appears to be improving
  - No unanticipated adverse device effects
  - Use according to recommendations has lower mortality and morbidity than surgery
- PAS is on track for data extraction to be completed by 31 December 2022
- Device is safe when used as designed and intended
  - Additional labeling changes to enhance safety are being pursued
  - Infants without successful anastomosis remain surgical candidates (device use does not limit subsequent surgery)
- The benefit:risk ratio remains favorable and we look forward to sharing results of full PAS data with the PAC to support your decision making

Questions?