FOOD AND DRUG ADMINISTRATION (FDA)

PEDIATRIC ADVISORY COMMITTEE
A PUBLIC MEETING

Virtual Public Meeting

September 17, 2021

ATTENDEES

PAC DESIGNATED FEDERAL OFFICER	FDA PRESENTERS
Marieann Brill, MBA, RAC, MT(ASCP)	Jian Connell, DNP, MSN, CPN
PAC MEMBERS	Lauren J. Min, PhD
Kelly Wade, MD, PhD, MSCE, Chair	**SPONSOR PRESENTERS**
Angela Czaja, MD, MSc, PhD	Ted Heise, PhD, RAC
Robert Dracker, MD, MHA, MBA, CPI	Bethany Slater, MD, MBA
Randall Flick, MD, MPH	Mario Zaritzky, MD
Peter Havens, MD, MS	**FDA PARTICIPANTS**
Bridgette Jones, MD, MS	Dionna Green, MD, FCP
Wael Sayej, MD	Shani Haugen, PhD
Richard Holubkov, PhD	Ethan Hausman, MD
Roberto Ortiz-Aguayo, MD, MMM	Vasum Peiris, MD, MPH, FAAP, FACC, FASE
Sarah Hoehn MD, MBe, FAAP	
Randi Oster, MBA	
Gianna McMillan, DBe	
PAC MEMBERS (Non-Voting)MEMBERS	
Ronald Portman, MD, FAAP	
TEMPORARY VOTING MEMBERS	
Gwenyth Fischer, MD, FAAP	
Jeffrey Lukish, MD, FACS, FAAP	
Jennifer Plumb, MD, MPH	

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CALL TO ORDER AND INTRODUCTION OF COMMITTEE

DR. KELLY WADE: Good morning and welcome. I would like to first remind everyone to mute your telephone lines when you are not speaking. For media and press, the FDA press contact is April Grant. Her email is april.grant@fda.hhs.gov. And her telephone number is 202-657-8179. For members of the industry and press, please sign in by sending an email to pac@fda.hhs.gov. Please direct all technical inquiries to the AV Support Team at virtual-wocc-support@fda.hhs.gov. This slide displays the link accessible for closed captioning. This link will also be shared in the chat section of the meeting throughout the day as well.

My name is Kelly Wade and I will be chairing today's virtual meeting. I will now call today's meeting of the Pediatric Advisory Committee to order. We will start by going over the meeting roster and introducing ourselves. When I call your name, please introduce yourselves. My name, as I have said, is Kelly Wade. I am a neonatologist at Children's Hospital of Philadelphia. We will now proceed with the PAC team. Angela Czaja.

DR. ANGELA CZAJA: Morning everyone. My name is Angela Czaja, one of the critical care physicians at Children's Hospital of Colorado.

DR. KELLY WADE: Dr. Dracker.

DR. ROBERT DRACKER: Good morning. My name is Bob Dracker. I am in Syracuse, New York. I am a pediatrician, hematologist and blood banker. I've been on the PAC for a while, just returned to it and I'm happy to be here. Thank you.

DR. KELLY WADE: Dr. Fischer.

DR. GWENYTH FISCHER: Morning. This is Gwen Fischer, a pediatric critical care physician from University of Minnesota Masonic Children's Hospital.

DR. KELLY WADE: Dr. Flick.

DR. RANDALL FLICK: Randall Flick, pediatric anesthesiologist and intensivist at Mayo Clinic.

DR. KELLY WADE: Dr. Havens.

DR. PETER HAVENS: Peter Havens, pediatric infectious diseases at the Medical College of Wisconsin and Children's Wisconsin in Milwaukee.

DR. KELLY WADE: Dr. Hoehn.

DR. SARAH HOEHN: Hi. Sarah Hoehn, pediatric critical care medicine and I also do pediatric palliative medicine, hospice, and pediatric ethics.

DR. KELLY WADE: Dr. Holubkov.

DR. RICHARD HOLUBKOV: Good morning. I'm Rich Holubkov. I'm a biostatistician, primarily a clinical trialist. My academic home is in the Division of Pediatric Critical Care at the University of Utah's School of Medicine.

DR. KELLY WADE: Dr. Jones.

DR. BRIDGETTE JONES: Good morning. My name is Bridgette Jones. I'm a pediatric allergy asthma immunologist and also in pediatric clinical pharmacology at Children's Mercy Hospital in Kansas City.

DR. KELLY WADE: Dr. Lukish.

DR. JEFFREY LUKISH: Good morning. Jeffrey Lukish here. Pediatric surgeon, Children's National, Washington, D.C.

DR. KELLY WADE: Dr. McMillan.

DR. GIANNA MCMILLAN: Gianna McMillan. I'm a bioethicist at Loyola Marymount University in Los Angeles and I'm also a patient family representative.

DR. KELLY WADE: Dr. Ortiz-Aguayo.

DR. ROBERTO ORTIZ-AGUAYO: Roberto Ortiz-Aguayo, child and adolescent psychiatry at Children's Hospital of Philadelphia.

DR. KELLY WADE: Okay. Ms. Oster.

MS. RANDI OSTER: Randi Oster. I am the consumer representative. I am a patient experience leader and represent the consumers on the panel.

DR. KELLY WADE: Dr. Plumb. Dr. Portman.

DR. RONALD PORTMAN: Hello. My name is Ron Portman. I'm a pediatric nephrologist. I head the pediatric clinical development program at Novartis Pharmaceuticals.

DR. KELLY WADE: And Dr. Sayej.

DR. WAEL SAYEJ: Good morning. My name is Dr. Wael Sayej. I'm a pediatric gastroenterologist at Bay State Children's Hospital in Springfield Massachusetts.

DR. KELLY WADE: Thank you, everyone, for joining the meeting today. Next slide. There are often strongly held opinions regarding the topic being discussed at today's meeting. Our goal is that today's meeting will be a fair and open forum for the discussion of the planned topic, ensuring individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand placed into the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. I will now pass it along

to Marieann Brill who will read the Conflict of Interest Statement.

MS. MARIEANN BRILL: Hi, Kelly. Good morning, everyone. This is Marieann Brill. But before I read the conflict of interest statement, we would also like to introduce our FDA people who will be on the line. And I will start. I am Marieann Brill, I am the Designated Federal Officer for the Pediatric Advisory Committee. Dionna.

DR. DIONNA GREEN: Good morning, everyone. My name is Dionna Green and I'm the Acting Director of the Office of Pediatric Therapeutics at FDA.

MS. MARIEANN BRILL: Ethan. Ethan Hausman. Vasum.

DR. VASUM PEIRIS: Thank you, Marieann. This is Vasum Peiris. I'm the Chief Medical Officer and Director for Pediatrics and Special Populations at our Center for Devices and Radiological Health.

CONFLICT OF INTEREST STATEMENT

MS. MARIEANN BRILL: Thank you. I will start now with my Conflict of Interest Statement. But before I start, I just want to say thank you so much and glad to have you with us today. The Food and Drug Administration is convening today, September 17, 2021, for a meeting of the Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972, Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, and the Food and Drug Administration Safety and Innovation Act of 2012. Today's meeting is a particular matter involving specific parties during which the committee will discuss the Flourish Pediatric Esophageal Atresia device. The chairperson for today's meeting is Dr. Kelly Wade.

With the exception of the industry representative, all standing and temporary

voting members of the committee are special government employees or regular government employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. Related to the discussions at today's meeting, standing and temporary voting members of the committee who are special government employees, or regular government employees, have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties and primary employment. These may include interests that are current or under negotiation. FDA has determined that members and temporary voting members of this advisory committee are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S.C. Section 208. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees, who have financial conflicts of interest, when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on the agenda for today's meeting, and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. With respect to the meeting's consumer

representative, we would like to disclose that Ms. Oster is participating in this meeting as a voting representative acting on behalf of consumers and not any particular organization, company or product. With respect to the meeting's patient representative, we would like to disclose that Dr. McMillan is participating in this meeting as a voting representative acting on behalf of patients, and not any particular organization, company or product. The consumer, and patient, representatives are special government employees and as such have been screened for conflicts of interest.

With respect to the meeting's Industry representative, we would like to disclose that Dr. Portman is participating in this meeting as a non-voting representative acting on behalf of regulated industry relevant to today's meeting. This representative is not a regular or special government employee, and as such has not been screened for conflicts of interest. This representative does not represent any particular organization, company or product. For today's meeting, Dr. Fischer, Dr. Lukish, and Dr. Plumb will be serving as temporary voting members. We would like to remind standing and temporary voting members that if the discussions involve any other firms or products not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such discussions and their exclusion will be noted for the record.

FDA also encourages all other meeting participants, including open public hearing speakers, to advise the committee of any financial relationships that you may have with the sponsor for today's meeting, its product and, if known, competing firms and products. This concludes my reading of the Conflict of Interest Statement for the public record. At this time, I would like to hand over the meeting to Dr. Wade. Thank you.

DR. KELLY WADE: Thank you, Marieann. We will now proceed with opening remarks from Dr. Dionna Green, the Acting Director for the Office of Pediatric

Therapeutics. Thank you, Dr. Green.

FDA OPENING REMARKS

DR. DIONNA GREEN: Thank you. Good morning, everyone. I am Dionna Green and I am the Acting Director in the Office of Pediatric Therapeutics in the Office of Clinical Policy and Programs in the Office of the Commissioner at the FDA. We are here today to discuss pediatric adverse reports following pediatric labeling changes as legislatively mandated. Specifically today we will be discussing one product from the Center for Devices and Radiological Health, or CDRH, which is the Flourish Pediatric Esophageal Atresia Device. I would like to welcome you and thank you all for joining us virtually today via webcast. I would also like to thank our DFO, Marieann Brill, and her team, Dr. Gerri Baer and her team, and our AV support staff for working hard to ensure that we will have a seamless meeting in this virtual setting. We ask in advance for your patience and flexibility if any technology related issues arise. Next slide.

I will be providing opening remarks starting with a few personnel updates, a summary of the web posted pediatric focused safety reviews, a presentation of the noncompliance letters since the last PAC meeting, and then I will end with a brief description of today's agenda. Next slide. We have three new members joining the Pediatric Advisory Committee.

The first is Dr. Robert Dracker, who has formerly served on the PAC as a standing member from June 2014 to June 2018, and as chair from June 2018 to June 2019. And has been reappointed to serve from July 2021 until June 2024. Dr. Dracker is the owner and medical director for Summerwood Pediatrics and is the founder and medical director for Infusacare Medical Services in Liverpool, New York. He serves as an attending pediatrician at

four health centers and has faculty appointments at several academic institutions. Dr. Dracker also holds multiple board certifications.

Next is Dr. Bridgette Jones who has previously served on the PAC as a pediatric health organization representative from February 2015 to June 2019. With her expertise in this role, and prior experience with the committee, she has been reappointed to serve as a member again from July 2021 to June 2025. Dr. Jones is board certified in pediatrics and in allergy immunology. She is the Assistant Dean of Student Affairs at the University of Missouri School of Medicine and is an Associate Professor of Pediatrics in the Divisions of Allergy Asthma Immunology and Pediatric Clinical Pharmacology, Toxicology, and Therapeutic Innovation at Children's Mercy Hospital and Clinic in Kansas City, Missouri. She also serves as the medical director for Children's Mercy's Office of Equity and Diversity.

And our third new member is Dr. Angela Czaja. She is an associate professor in the Division of Critical Care, Department of Pediatrics, at the University of Colorado School of Medicine. She received her M.D., from the University of Pennsylvania and Ph.D. in Pharmaceutical Outcomes Research from the University of Colorado School of Pharmacy. Dr. Czaja completed her fellowship in pediatric critical care at Seattle Children's Hospital and the University of Washington. She is board certified in pediatrics and pediatric critical care. We would like to welcome our new PAC members and thank them for serving on the committee.

My last personnel update is related to our office, the Office of Pediatric Therapeutics or OPT. Dr. Susie McCune, who has served as the director of OPT since 2017, retired from the FDA at the end of July after 18 years of federal service. Dr. McCune is a pediatrician and neonatologist by training and practiced academic medicine for several years at Johns Hopkins and Children's National Medical Center, as well as conducted research at NIH prior to joining the FDA. Dr. McCune joined FDA in 2003, and originally worked in the

Division of Pediatric Drug Development in what was the Office of Counter Terrorism and Pediatric Drug Development in CDER. She then became the deputy director in the Office of Translational Sciences in CDER from 2010 to 2017. We would like to sincerely thank Dr. McCune for all that she has done on behalf of neonates, children and adolescents, and for her outstanding service to the FDA, to the Office of Pediatric Therapeutics and to the Pediatric Advisory Committee. Next slide.

Next, I would like to highlight the web posted reviews. Since we did not have a PAC meeting in the spring, we are including the reviews for both the spring and the fall of 2021. As listed on this slide there are 12 CDER products, seven CBER products and nine CDRH products. The docket for comments on these reviews is open and will remain open until September 24, 2021. Next slide.

I am required by the legislation to report on PREA non-compliance letters. There are currently two for CBER and 91 for CDER. The websites listed on this slide provides the list of sponsors, the products, a copy of the non-compliance letter, the sponsors response, if available, and the status of the PREA requirements. So, for example, whether the requirement has been released, replaced or fulfilled. Next slide.

Since the last reporting on the non-compliance letters at the September 2020 PAC meeting, there are no new letters for CBER and 21 new letters for CDER. Next slide. The information on these 21 new letters for CDER is listed here on this slide. Next slide. And the information continues here onto this slide. Next slide. So now in terms of the rest of the agenda for today's meeting, the meeting will proceed as follows. We will first have a presentation from representatives from FDAs CDRH and this will be followed by the sponsor presentation. Next slide. The open public portion of the meeting will start at 11:30 a.m. This will be followed by a lunch break at approximately 12:30 p.m. The meeting will resume at 1:00 p.m. for committee

discussion and vote and we are scheduled to adjourn the meeting at approximately 3:00 p.m.

And with that, I would like to thank you for your attention and welcome you to the fall 2021 PAC meeting. I will now turn the meeting back over to our chairperson, Dr. Kelly Wade. Thank you.

DR. KELLY WADE: Thank you, so much, Dr. Green. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Advisory Committee meeting the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages all participants to advise the committee of any financial relationships they may have with the firms at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation it will not preclude you from speaking. We will now proceed with the presentations from the FDA.

FDA PRESENTATION

MS. LAUREN MIN: Good morning. My name is Lauren Min and I am an epidemiologist in the Gastroenterology and Endoscopy Devices Team. Jian Connell, the senior MDR analyst and I will be presenting a summary of the third annual update for the Flourish Pediatric Esophageal Atresia Device which includes a review of the published literature, post approval use and medical device reports. Before we get started I'd like to provide a quick

overview of the HDE program which is for devices intended to benefit patients in the diagnosis or treatment of diseases affecting less than 8,000 individuals in the U.S. per year. The criteria for HDE approval is presented on this slide. The Flourish device is intended to treat esophageal atresia which is a developmental arrest of the esophagus resulting in the absence of normal esophageal lumen.

Of the five recognized EA types Flourish is to be used in patients with Type A esophageal atresia without tracheoesophageal fistula and also in patients with Type C EA for whom a concurrent TEF has been closed as a result of a prior procedure. The current standard of care for EA includes surgical repair via thoracotomy or thoracoscopy to create an anastomosis between the two esophageal segments. Risks of surgery include the risks of anesthesia, post-op pain, leak and stenosis of the anastomosis, gastroesophageal reflux, esophageal dysmotility, and fistula recurrence. In addition, deformities of the thoracic wall can occur later in life and can include shoulder weakness, winged scapula, and scoliosis. If surgical repair is unsuccessful, colonic, gastric, or jejunal interposition may be performed.

The indications for use is stated on this page. Instead of reading it word for word, I will just highlight that the Flourish device is used to create an anastomosis in infants up to one year of age with EA in which the esophageal segments are less than four centimeters apart. The Flourish device consists of an esophageal catheter and a gastric catheter with distal ends of both containing magnets. In a candidate infant the distance between the atretic segments is assessed under fluoroscopy. After identification of the pouches, the esophageal and gastric catheters are inserted orally and through the gastrostomy stoma and advanced until the magnets are located at the distal end of each pouch. Within three to 13 days the traction caused by the magnets allow the two pouches to approximate and daily chest x-rays are taken to assess the distance between magnets. Once approximated, the surrounding tissues grow together while the tissues between

the magnets necrose causing the anastomosis. After an anastomosis has been confirmed the magnets are removed and an OG or NG tube is placed for one to three days.

FDA relied upon data from two articles to grant the HDE submission. In the first article nine patients from a single center in Argentina were treated with Flourish. All nine achieved anastomosis and were reported to be ingesting a normal diet long-term. However, eight of the nine patients developed anastomotic strictures that required dilatation. Two of these patients developed intractable stenosis and underwent stent placement and one patient underwent several dilatations and stent placement ultimately requiring surgical re-anastomosis. The second article described two cases. Both patients achieved anastomosis but both also developed strictures. For the remaining patients, FDA relied upon information submitted in five emergency use case reports. All achieved anastomosis but three patients developed stricture as well.

In totality we had pre-market data from 16 patients, all of whom achieved anastomosis, but 13 developing anastomotic strictures that required intervention. This stricture rate was higher than what was reported for standard of care surgical repair which was estimated to be 30 to 40 percent. However, anastomotic repair could occur earlier with the Flourish device and avoid surgical complications. Therefore, it was concluded that the probable benefits of earlier anastomotic repair and fewer surgical complications outweighed the risks of a higher anastomotic stricture rate requiring balloon dilatation and/or esophageal stenting in the appropriate patients and thus the HDE was granted. Next, we will present FDA's review of post-approval data during our reporting period between June 1st, 2020 and April 30th of 2021. First, we conducted a systematic literature review on the Flourish device using the methods listed on this slide.

Two articles met our criteria which described a total of four patients. In the

Wolfe study two of the three patients treated with Flourish achieved anastomosis but more frequently required dilatations to treat anastomotic strictures. The Liu study described an infant who successfully achieved anastomosis using customized magnet rings that are similar to, but not the same as Flourish. Although our literature search resulted in only two papers describing four patients, the safety and effectiveness findings in both publications are not different from what was previously known at the time of the HDE approval. As a condition of device approval, a Post-Approval Study or PAS, was designed to obtain longer term data on strictures and other clinical outcomes.

The PAS is expected to enroll 20 patients who are followed for up to two years post-Flourish treatment. The primary outcomes are stricture formation at the anastomotic site, peri-anastomotic leaks, and adverse events related to the device or procedure. And the secondary outcome is successful anastomosis formation. During our reporting period nine patients were treated with Flourish and all were commercial uses. Thus, zero PAS patients were treated during this period. Due to a lower than expected rate of patient enrollment, the post-approval study was revised in 2020 to allow retrospective data collection from medical records. This revised PAS is currently underway and is expected to be completed in December of 2022. This table shows a high-level overview of the anastomosis data we have received on the nine patients who were treated during this reporting period. All had a pre-procedure atretic gap less than or equal to four centimeters and anastomosis was achieved in six of the nine patients. Information on the type of esophageal atresia was available for four of the nine patients.

On the next slide I will summarize the anastomosis information to date. In the cases prior to device approval all 16 patients had successful anastomosis formation. However, of the 31 patients who have been treated to date, post-approval, the rate has been lowered at 58 percent. This can be further broken down into anastomosis rates in PAS patients which is 33

percent and in non-PAS patients which is 64 percent. Of the nine patients who were treated during this reporting period the anastomosis rate is 67 percent. Currently we do not have complete information on stricture formation in these nine patients. However, some experienced adverse events that were reported in the MDRs. Next, Dr. Connell will present the MDR update.

DR. JIAN CONNELL: Thank you, Dr. Min. My name is Jian Connell. I am a senior MDR Analyst for the Gastroenterology and Endoscopy Devices Team at FDA. I'll be presenting an update regarding medical device reports including a discussion of new adverse events as well as their potential mitigations. This slide is the MDR disclaimer. Rather than reading it word by word, I want to point out that there are strengths and limitations of MDR data as described here. I will start by providing an overview of the MDR updates. Seven MDRs were received in the reporting period. The time to event occurrence ranged from the same date to 35 days. In five out of seven patients, anastomosis was not achieved. There were four new adverse events identified during this period which included two esophageal perforation cases, one of which was an unconfirmed perforation.

One case of tracheoesophageal fistula was identified after the Flourish removal, and one case of a device placement failure possibly due to insufficient magnet strength. Based on the adverse events, FDA requested additional information from the manufacturer. Next, I will discuss each new adverse event followed by the FDA actions and the mitigations taken or proposed by the manufacturer.

Perforation case number one: a physician reported an under one year old patient with an esophageal perforation in the lower esophageal area. Post-Flourish device placement the magnets were repositioned in radiology as the distal magnet seemed to have fallen out of place. The gastric feeding tube was left in the distal esophageal pouch during the device

indwell period. The gap was reduced to 2.2 centimeters by day three. However, on day four the patient started to have a fever. A contrast study showed some contrast drained into the right bronchus, likely indicating perforation of the distal pouch. This prompted the physician to remove both magnets without further incident. A chest tube was placed and a thoracotomy was scheduled for further assessment and treatment. The root cause of the perforation has not been identified.

Perforation case number two: a physician reported a potential esophageal perforation in a seven-month-old patient. At the time of the procedure the gap distance appeared to be around four centimeters. The physician decided to leave the inner catheters in the locked position while pushing on the catheters, causing the magnets to come closer together. Because when the inner catheters were unlocked the magnets would regress back and the gap distance would be further away. On one occasion the magnet regressed back to five centimeters. The physician also introduced a feeding tube into the lower esophageal pouch for more support of the lower magnet.

On day 21 of the device placement the magnets were touching. About a week later the esophagram indicated the magnets had likely perforated through the esophageal pouch. The magnets were then removed in the operation room and a nasal jejunal tube was placed. An endoscopy was performed to dilate the anastomosis area under fluoroscopy but the procedure was unable to confirm if a perforation occurred. The physician further stated that magnet would not have come together without the pushing and the locking of the device. However, the Cook representative stated that this was the first time any user had left the magnets in longer than 13 days. This was also the first time that the method of putting tension on the inner catheters and locking both catheters had ever been done before. After receiving the reports of perforations, FDA requested additional information from the manufacturer regarding the root cause analysis

and mitigation strategies.

In response to FDA's request for information regarding the perforation adverse events, Cook submitted a HDE supplement for labeling revisions which was approved in December of 2020. The labeling revisions include the following: added potential complications of perforation or leak and of death during the device indwelling period, added two warnings regarding improper placement of feeding or gastric tubes, as well as applying force onto esophageal pouches could result in subsequent perforation. And clarified the locking status of the catheters during indwelling period that at least one of the inner catheters should be in the unlocked position. Case number 3 TEF: a physician reported a 4.4-month-old patient regarding a life threatening tracheoesophageal fistula after use of the Flourish device. During a Flourish device placement, the physician and interventional radiologist decided to leave a wire guide in the lower Flourish catheter for support.

The manufacturer representative reminded the physician that leaving the wire guide in place could add friction and weight to the inner catheter. The magnet was repositioned daily. On day nine the physician applied force to the magnets to try to bring them together and achieve anastomosis that same day. The manufacturer representative warned that the tension applied could cause a perforation. On day 14 the esophagram looked good and there was no leak. The device was removed that day. Four days after the device removal the patient started to have respiratory issues. A surgical consult indicated a concern for the presence of TEF. The patient was transferred to a sister hospital. A large TEF was confirmed by both a bronchoscopy and an esophagoscopy. The patient's condition was decompensated and required an emergency thoracotomy surgery. The patient's medical history showed that the patient was born with a pure esophageal atresia.

The manufacturer investigation concluded that the most likely root cause of the

TEF was related to the improper use of the device, specifically the user applied force to the device to try to bring the magnets together. In response to the FDA's request of MDR on TEF Cook stated that a definite root cause was not identified. Per the report, the esophagram looked good upon Flourish removal with no apparent leaks. However, a TEF was identified four days after Flourish removal. It's possible that the Flourish device could cause an acquired TEF. But noted that instead of letting the magnets make a progressive attraction, the user applied force on the magnets which could predispose the esophageal pouch to a perforation. Therefore, Cook identified the most likely root cause to be improper use of the device by the user. Cook intends to submit a new HDE supplement for the labeling change to include the potential complications of TEF.

Case number 4: insufficient magnet strength. A physician reported a Flourish device placement failure in eight-month-old patient. During the procedure the physician tried to place the Flourish magnets but was not successful. It was reported that the patient's lower esophageal pouch was very thin and short and the magnet kept sliding out after placement. The procedure was aborted. Per the user, the atretic gap distance was 2.3 centimeters which was within the range of indication for use but could not approximate the pouches less than two centimeters without some tension. The physician tested the magnets ex vivo and found that they did not connect until they were about 1.5 to 1.7 centimeters apart just as observed during the aborted clinical procedure.

The device was not returned to the manufacturer for evaluation. So the manufacturer tested a device from the same lot and found that the magnets showed attraction towards each other when moving four centimeters, but do not fully pull together at this distance. This is the expected behavior of the device, per the manufacturer. In the following slide, I will explain the expected behavior of the device. In response to FDA's questions regarding the

MDR on 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. This intrinsic feature 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 a perforation.

To maintain safe use, Cook noted that the device must not provide excessive magnetic compression pressure such that the tissue between the magnets necroses before an adequate fusion of the esophageal pouches to achieve anastomosis which may lead to anastomotic leaks. Based on the additional information from Cook, FDA proposed an interactive meeting with Cook to further understand the device characteristics, as well as discussing their mitigation strategies. At the meeting, Cook presented a study by Lambe, et. al. (2014). The study quantified the magnetic pressure required to successfully achieve gastrointestinal anastomosis from porcine survival models. Study results show that an optimal compression pressure is between 30 to 60 Newton (N) per square centimeter and should not exceed 60 N per square centimeter at a two-millimeter inter-magnet separation.

Based on this optimal compression pressure Cook set the Flourish device to exert a mean compression pressure of 37.3 N per square centimeter. Cook stated that due to the exponential relationship between force and distance a slight increase in force at small distances has very little impact on force at larger distances. This could result in higher potential for perforation at smaller distances without significantly impacting forces at larger distances. Cook also identified multiple clinical factors that could potentially impact the effectiveness of magnet attraction and subsequent anastomosis such as patient anatomy, length of esophageal pouches, location of PEG tubes, and fibrous tissue from prior surgeries. Given the available clinical data and the potential for increased risk of perforation and anastomotic leak that may be associated with increase in magnet size, Cook does not consider that a design change to the Flourish device

is warranted at this time.

Based on the information provided by Cook, FDA suggested that Cook conduct a thorough review of the current labeling, then provide a comprehensive mitigation plan. After the meeting with FDA, Cook proposed an additional action plan as discussed at the FDA meeting. Cook will provide a new HDE supplement to improve the current labeling, including potential new complications, clarification of repositioning the device after placement, additional warnings of improper use of device and consequences, editing the device description, and update the physician training. Regarding the clinical factors, currently there is limited information to support specific recommendations. Cook stated that it's difficult to recreate patient specific situations in a benchtop model. For this reason, patient specific factors will be assessed at the conclusion of Cook's post-approval study. FDA and Cook are currently engaged in discussions regarding the details of the proposed mitigation plan.

In summary, there were new serious adverse events of esophageal perforation and tracheoesophageal fistula identified in this reporting period. Recurrent improper use of device was observed based on these adverse event reports which was inconsistent with the instructions for use. Additionally, the applied force on the esophageal pouches could potentially cause the perforation. Cook identified multiple clinical factors that could potentially impact the effectiveness of magnet attraction and the subsequent anastomosis. Finally, the device magnets have an exponential property such that a slight increase in force at small distances has very little impact on force at larger distances but could result in higher potential for perforation at smaller distances. The committee will be asked to comment on the types of labeling changes that may reduce the risk of these serious adverse events.

The committee will also be asked to comment on labeling changes to identify factors that could impact device effectiveness when there is limited information to support

specific recommendations regarding those variables. Next, Dr. Min will present the conclusions.

DR. LAUREN MIN: Flourish was approved in 2017 with limited clinical data from literature and emergency use cases demonstrating successful anastomosis formation in all described cases. However, post-approval data from nine treated patients in the current reporting period show an evolving benefit risk profile relative to when the device was approved. Successful anastomosis formation was observed in six of the nine patients compared to 16 of 16 patients in the pre-market data. Reported safety uses during this period include perforations, TEF, stricture formation, and insufficient magnet strength. Limited data in non-PAS patients does not allow for definitive conclusions. We expect to gain a clearer picture of the device's benefit-risk profile with completion of the PAS and continued evaluation of non-PAS patients. FDA still finds it reasonable to conclude that the probable benefit to health outweighs the risk of injury or illness when used as indicated.

Our analysis considers the probable risks and benefits of currently available devices or alternative forms of treatment. With Flourish, 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. However, given the serious adverse events observed in this reporting period, FDA and Cook are discussing potential labeling and training revisions to reduce this risk. Therefore, FDA recommends continued surveillance of the Flourish device, including evaluation of the annual distribution number, post-approval study results, MDR review, literature review, and any additional device or labeling changes or manufacturer communications. We plan to report this information to the PAC in 2022.

Next, we will introduce the voting questions that will be presented again in the

afternoon session when voting takes place. Please note that there will be time for clarifying questions before panel voting. Question one: Recurrent improper use of the device was observed in the new serious adverse events. Also, the attractive force of the magnet increases as the distance is reduced. Does the committee agree that additional warnings about improper device use, including excess user manipulations of the device, and explanation of the magnet behavior would address and mitigate the risk of perforations or TEFs? Question two: There are multiple clinical factors that can impact the effectiveness of the anastomosis. Does the committee agree that physicians should be given additional information regarding the clinical variables to better identify suitable candidates for treatment with the Flourish device?

Question three: The FDA will report on the following to the PAC in 2022: annual distribution number, PAS results, MDR review, and literature review. Does the Committee agree with the FDA's plan for continued surveillance of the Flourish device? This concludes FDA's presentation.

DR. KELLY WADE: Thank you so much. Before the sponsor presentation, I would just like to introduce or have Dr. Plumb introduce herself as a temporary voting member of the PAC. Dr. Plumb, could you unmute and introduce yourself?

DR. JENNIFER PLUMB: Hello there. Turn on the video as -- oh, I'm not able to start a video. Okay, introducing myself. I'm a pediatric emergency medicine physician at the University of Utah, associate professor of pediatrics. My research interests include opioid overdose prevention, use of ultrasound in the emergency department, and patient safety. Thank you for the opportunity to join.

DR. KELLY WADE: Thank you for being with us. For the members of the PAC, please save your questions for now. You will have an opportunity to ask clarifying questions after the sponsor's presentation. And I will now turn it over to Cook Medical for their

presentation.

SPONSOR PRESENTATION

DR. TED HEISE: Thank you, Dr. Wade. Let me get the presentation pulled up. I'm sorry, I need to do that a certain way so you can hear the sound. Let me try one more time. Can you see our slides okay with the title slide?

DR. KELLY WADE: Yes, we see the title slide.

DR. TED HEISE: Thank you very much. And good morning. I'm Ted Heise, vice president of regulatory and clinical at MED Institute. MED is a Cook Group company that focuses on research and development of new medical technology and is a sister to Cook Medical. We thank you for the opportunity to present our experience with the Flourish Pediatric Esophageal Atresia Device. We are pleased to be here today and are happy to provide information to support your deliberations on this product. An important context for discussion today is that Flourish is a device that may prevent the need for surgery. It may not work for every patient, but in our commercial experience to date we are not seeing safety issues when it is used as intended. From your briefing material as well as the FDA presentation you should appreciate that the Flourish device was developed for a very small patient population.

As such, there are known disincentives to commercialization that often prohibit the undertaking of such projects. I'm very proud to work for a company that is willing to pursue options to serve the needs of these few patients despite the challenges. In making this product available Cook has put considerable effort into doing so with a focus on safety. For example, by requesting and reviewing imaging to assess suitability each time a device is requested, as well as providing training and in person support of each case. Let us turn now to our agenda for today. I'll start with a brief company overview with our commitment to unmet

needs. And then we are privileged to have a couple of expert physicians with us today who will describe for you the clinical need and the impact of open surgery and the expected benefit of Flourish device use.

We'll then go through a high-level summary of the post-approval experience to date, talk about implemented as well as proposed labeling changes, and then conclude with an update on the post-approval study itself. Founded in 1963, Cook Medical is a family-owned multi-national medical device manufacturer with world headquarters in Bloomington, Indiana. Our company employs over 12,000 employees around the world, 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. Cook has a long history of commitment to pediatric patients, initially helping craft the enabling legislation for HDEs, a common pathway for pediatric devices as well as contributing to the implementing regulation.

We pioneered the first HDE approval with the Harrison Fetal Bladder Stent. We've provided comments on all amendments to the HDE regulation, we've submitted an accepted NEST project to evaluate the process of collecting real world data in support of a pediatric device approval. And we are actively pursuing additional small market pediatric products. For example, within the binational Harmonization By Doing for Children program collaboratively with colleagues and other stakeholders in Japan. And then finally, or most recently, we've demonstrated commitment with approval of the Flourish Atresia Device, a minimally invasive option for select infants that avoids need for major surgery and is the focus of our presentation and our discussion today. I'd like now to present a patient vignette for you.

VIDEO: Hello, I am Dr. Mario Zaritzky. I am a former Argentinian pediatric surgeon working now as a pediatric radiologist in Chicago. Back in Argentina in 1995 I was

treating patients with the traditional method of open chest surgery for esophageal atresia, but I had the feeling that it has to be something else less aggressive to treat those patients. So I start looking for a company who will share my passion, my vision, my dream of doing that. And it was a very difficult task until I crossed path with Cook. We were able, with Cook, to come up with an excellent device to treat these patients. Look, I can talk forever about this device. Probably you already feel my passion and my enthusiasm about it but I think that there is a better way by hearing from a family that was impacted by this product.

Basically, it was a waiting game. Having to wait for a definite decision is excruciatingly painful. You're leaving one child at home, you can't go to work. You're just -- you sit in this room completely helpless with your tiny, tiny little baby. Unfortunately, you don't know if it's actually going to be an esophageal atresia until your child is born and they take the x-ray and they're like, this is definitely what it is. Esophageal atresia is very rare. It only occurs maybe one in 5,000 births or deliveries. Babies like Annalise who were born with no connection, have two ends of their esophagus that don't meet. And hers was about three centimeters. Typically, we would open the chest and go in and stretch the two ends together with stitches. I had heard about using magnets to perform the anastomosis. I found the articles from Dr. Zaritzky and I called him and talked to him about it.

Dr. Zaritzky came to us about, like, close to 15 years ago. He came up with this concept of putting a magnet through the stomach port and putting a magnet through the mouth, and those two magnets sort of coming together at over a period of seven to 10 days would then be fused and the baby could then be able to swallow and drink. That's the whole point of what we do is to give patients the type of technology that they need in order to serve them. The first time I saw the device was a week or so before the procedure. We're all on pins and needles as this is the first time it's ever been done in the United States. We're taking the esophagus that's

never been operated on before and we're fusing it without surgery. This is novel. This is cool. This is new. Thirty-six hours after the magnets were placed, we found that they were actually together, they were connected.

Once the magnets were out, that day, she was taking milk and just sucking it down like she'd been doing it all her life. And now we have this beautiful little girl who's running around that wants to eat pizza all the time. It meant less time in the NICU, it meant a less invasive procedure. I just couldn't see anything but positives. The device is not for a lot of cases. It's a humanitarian device, which means that at the most you might have three to four cases per month. Why do it? I think the impact to the patient you can see, and the Cook philosophy is that sometimes just the bottom line doesn't matter. What matters is you get some of these impactful devices out to the patient and do what's right. **(END OF VIDEO)**

DR. TED HEISE: Dr. Zaritzky.

DR. MARIO ZARITZKY: Hello. I am Dr. Mario Zaritzky. I am a former Argentinian board-certified pediatric surgeon and pediatric radiologist working now as a board eligible pediatric radiologist at the University of Chicago. As you heard in the video, working with Cook, we were able to come up with an excellent device to treat pediatric patients with esophageal atresia. And that's the device that we are here to talk about today. To speak about the background of pediatric esophageal atresia and the clinical need for Flourish device I would now like to introduce Dr. Bethany Slater.

DR. BETHANY SLATER: Thank you, very much. I am a pediatric surgeon at the University of Chicago. And can you go to the next slide please. There are a number of complications that can occur after a surgical repair of esophageal atresia either with or without a tracheal esophageal fistula. The first being an anastomotic leak which has been reported in 13 percent to 16 percent of patients repaired surgically. You can see in the esophagram at the

bottom of the screen the leak after contrast is ingested. Additionally, a stricture can occur in up to 80 percent of patients that have been surgically repaired. And this can also be shown in another esophagram at the bottom of the screen. In these patients it's very common to have to have repeated balloon dilations. And finally, a recurrent fistula can be seen in about 3 percent to 14 percent of patients that underwent surgical repair.

In addition to these shorter-term complications, a number of long-term complications also occur such as gastroesophageal reflux, tracheomalacia, or a variety of quality of life issues. This is a systematic review looking specifically at complications of surgical repair after tracheoesophageal atresia repairs. This was looking at 10 years after surgical repair. And they found that there was a mortality rate of nearly 5 percent and additional surgery was required in 8.6 percent of these cases. Specifically looking at long gap esophageal atresia this really makes up a very technically challenging group of patients. There are a large variety of surgical techniques that can be used but with all of these techniques they require multiple operations, typically repeated anesthetics, and prolonged operative times. And all of these factors lead to significant physiologic stress to the patient.

This is a diagram of the Flourish device which can be used as a nonsurgical alternative to esophageal atresia repair. And there is an oral catheter and a gastric catheter with a port for suctioning. And in the gastric portion, an area for feeds that can be installed after the magnet is placed. And I'll hand it over, back to Ted, to discuss some of the benefits of the Flourish device.

DR. TED HEISE: On the slide in front of you, you can see a listing of some of the expected benefits from use of this minimally invasive procedure. It does avoid an invasive surgical procedure in many cases, it avoids dissection on the esophageal pouches with commensurate potential for decreased dysmotility of esophagus, decreased risk of injury to

recurrent laryngeal nerve, and no need for a Azygos vein ligation which prevents a rare potential for hemorrhagic events. And this also may be particularly beneficial treatment option for patients with cardiac or other anomalies. Now we'd like to present an overview of the post-approval experience through July of 2021. The device, through that period, had been -- has been used in 33 infants including seeing one compassionate use prior to commercial distribution. Three patients have had -- three of these 33 infants have had two devices used. Of those 33, eight have occurred in four hospitals in Canada under special access provisions and 25 have occurred in 16 hospitals in the U.S.

Importantly, the primary safety outcome of major adverse event and the secondary end point for evaluation of probable benefit, in other words successful anastomosis, are known for all 33 patients. Here's a tabulation of the results for those parameters through the end of May 2021. And I am not going to go through this in detail but I'd like to call your attention to several things. Firstly, you can see that the number of cases is relatively small, roughly 10 per year. Secondly, you will see that the success has not been 100 percent as FDA indicated. However, the rates do appear to have been increasing year over year. And then in the last column you will also note that there were several adverse events observed in the cases to date. FDA gave you a very nice overview of those cases and I will touch on them briefly in the subsequent slide.

Thinking about the factors that can contribute to formation of an anastomosis there are several that likely are influences. And these are expected to include prior thoracic surgery, patient anatomy, connective tissue, or tethering of pouches to adjacent structures. As we collect more complete data by way of the PAS, we expect that the information may be helpful in better understanding factors that can affect success. And importantly, infants without successful anastomosis remain surgical candidates and the device does not limit subsequent

surgery. FDA described for you a complaint regarding magnet forces, and that complaint as well as questions from FSA prompted a company review of the magnet forces. The design requirement for this technology was based on a published paper from Lambe which described that compression pressure at a distance of two millimeters should not exceed 16 N per centimeter squared.

This is because higher compressive pressure may increase the risk of perforation and/or anastomotic leaks by an accelerated disruption of the tissue between the magnets as they come together prior to the tissue being able to reform around the magnets and create a complete anastomosis. For the Flourish surface area of .104 centimeters squared, the force at two millimeters, therefore, should be less than six N. From measured forces, the upper 99 percent confidence limit is the two -- the two-millimeter distance is just under five N. This provides a reasonable safety margin under the six-N limit from data Lambe has published. We also want to note that the force decreases exponentially with separation. You will see, for example, at four centimeters separation that there is a very small force. And furthermore, an increase in magnet strength would move this entire curve upward, causing a potentially unsafe increase in forces at two millimeters.

Ex vivo, the magnets do visibly attract each other at distances greater than four centimeters, as you can see in the video that I'm showing. This confirms that the magnetic fields are, indeed, interactive. Factors that could impact the force of magnetic attraction include the particular alignment of the magnets as well as proximity to metallic objects. And importantly, in a clinical use this same magnet design formed an esophageal anastomosis in the premarket patients. Successful anastomosis have been achieved in infants with gap lengths up to four centimeters. Returning to the topic of safety, four MDRs filed in 2020 and 2021 related to esophageal pouch leak, potential perforation, perforation, or possible perforation with trachea

esophageal fistula. In every case the physician exceeded recommended device use in one or more of several different ways.

These include leaving the G-tube advanced into the lower esophageal pouch, applying added force or tension to the magnet catheters beyond what the magnets themselves provide, as well as locking the magnets with tension applied physically to those magnets. I'd also like to note that it is unclear based on the available information whether the case with the TEF may have actually had an unappreciated pre-existing defect. In response to the complications and adverse events that were reported to the company changes were made to address these potential risks, particularly by strengthening warnings against abnormal use. These were approved by FDA in December of this past year. Briefly, these changes expanded the list of potential complications during device indwell to include perforation leak of one or both esophageal pouches or the anastomotic site which could result in additional procedures and/or death.

The changes also 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. The changes also clarified the appropriate locking status of the oral and gastric catheters during indwell. Furthermore, Cook has proposed to FDA additional labeling changes intended to further enhance safety. Briefly, these include the 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, and clarifications to IFU language regarding repositioning the magnets during indwell. To sum up the post-approval experience, the rate of successful anastomosis has increased from 43 percent to 57 percent, to 67 percent year over year, suggesting that changes in labeling have improved case selection.

The device appears to be safe when used as recommended. Balloon dilatation, though not uncommon, is also often necessary for infants whose atresia has been treated surgically. Several cases of esophageal leak or perforation were associated with use of the device well outside of recommendations. None occurred when labeling was followed versus a 13 to 16 percent rate observed following surgery. There were no unanticipated adverse device effects and no patient deaths as compared to the published 5 percent rate with surgery. Importantly, infants without successful anastomosis remain candidates for surgery and we conclude that the benefit risk ratio remains favorable. Regarding an update on the post-approval study, as FDA described, the company is required to collect additional data from 20 patients by the end of 2022 for a final report to FDA by the end of Q1 2023.

As FDA noted, patients were initially enrolled under a traditional investigative study design. Enrollment challenges prompted a change to a more pragmatic study design, specifically a real-world data collection. Toward the end of this past year, FDA approved the revised study plan. In following months, a central IRB approved the revised study plan, and in February through April of 2021 five hospital IRBs approved revised study plan. To date, nine patients have been included in the PAS. The six enrolled under the traditional investigative study design and three enrolled under the pragmatic real world data study design. All since the end of the 2021 reporting period. This represents nearly 50 percent of the required total of 20. Seven of these nine patients have met a study exit point and two patients remain active study participants.

We expect progress to accelerate now that many HCPs have been contacted to participate and also now understand the new approach. We are projecting four cases within the coming months. Two of these have actually already been collected and an additional 11 cases over the first part of 2022. With the nine cases already collected, we expect these to bring our

total to the required 20 and the additional case data from these procedures will likely inform improvements in future case selection and labeling. For our final summary and conclusions, the Flourish device provides an important minimally invasive treatment option for appropriate infants, often avoiding the need for major surgery. Our clinical experience to date has been largely favorable. The rate of successful anastomosis, while less than 100 percent, does appear to be improving.

There have been no unanticipated adverse device effects and use according to recommendations has lower mortality and morbidity than surgery with no mortality. The PAS is on track for data extraction to be completed by the end of 2022, as expected. The device is safe when used as design and intended. Additional labeling changes to enhance safety are being pursued and infants without successful anastomosis do remain surgical candidates. Finally, the benefit risk ratio remains favorable in our view and we look forward to sharing results of the full PAS data with the PAC in the future to support your decision making. Thank you, very much.

CLARIFYING QUESTIONS

DR. KELLY WADE: Thank you. Before we open discussion of clarifying questions, I would like to call on Dr. Hausman from the FDA.

DR. ETHAN HAUSMAN: Hi. This is Ethan Hausman. I could not unmute this morning. I am representing the Division of Pediatric and Maternal Health and my background is in drugs and devices. And I'm a pediatrician and a clinical pathologist and a transfusion medicine specialist. Thank you**.**

DR. KELLY WADE: Thank you. We're happy to have you. We will now

proceed with clarifying questions regarding the presentations by the FDA and the sponsor. I will remind you to use the raise the hand button at the bottom of your screen so that I will know to call on you. I will first call on Dr. Robert Dracker.

DR. ROBERT DRACKER: Thank you, Kelly. This is Bob Dracker, member of the PAC. I love this device. It's been very cool to consider previously and it would be wonderful if it was used routinely with low incidence of complications. The one question I have though is, once anastomosis is achieved and since it looks like stricture is still a problem in some cases, has there been consideration given to placement of a stent of some sort once anastomosis is achieved to prevent subsequent stenosis?

DR. MARIO ZARITZKY: Please, can you repeat? Because you were cutting out. At least in my computer I couldn't hear very well your question.

DR. ROBERT DRACKER: Sure, no problem.

DR. MARIO ZARITZKY: Sorry.

DR. ROBERT DRACKER: My question was that once anastomosis is achieved utilizing your device and since stenosis following anastomosis is still a potential complication has there been consideration to the placement of a stent of some sort once anastomosis is achieved to avoid the problems with stenosis?

DR. TED HEISE: To respond to your question I would suggest firstly that the magnets, once joined, are left in situ for several days to allow (inaudible) in that new anastomotic tissue. Once that occurs, they are removed. The tissue, I would expect, is rather sensitive still at that point and I'm not sure a stent would be the appropriate option. We certainly have not suggested it or considered it. But it might be nice to hear from Drs. Zaritzky or Slater, whether they have thoughts on that point.

DR. MARIO ZARITZKY: First of all, thank you for your question. It shows

good insight, knowledge of the problem. To be honest, we are considering maybe doing something in the future. Not yet. We don't want to add any conflicting data to our experience. But also, once the anastomosis is completed by the magnets and the magnets are removed, usually we leave a NG tube in place. Which, somehow it's acting as a stenting device or at least to keep the region open. And I totally agree with Ted that I would be very afraid of placing a stent which has a, I will say strong radial force, that once you deploy the stent you cannot control through a newly anastomosis made by magnets or in any case by surgery. I mean, the same concept can apply for surgical repair. I mean, I don't think that any surgeon is going to leave a stent after a surgical anastomosis immediately.

And also, there is more problems. There are no very well known or very -- there are no deep status about using stents, cover stents, and retrievable stents in pediatrics. The stents in pediatrics are -- usually they are stent intended to use in other places of the body for adults, like for example binary stents, for adults to use in the esophagus of kids. So there is many layers of complications if we tried to do that.

DR. KELLY WADE: Dr. Dracker, is this a follow up --

DR. ROBERT DRACKER: Yeah, I --

DR. KELLY WADE: -- to this specific conversation or a new question?

DR. ROBERT DRACKER: It was follow-up to that. And did you --

DR. KELLY WADE: Go ahead.

DR. ROBERT DRACKER: To be very honest with you I was not suggesting the placement of a stent immediately following anastomosis achievement. But because of the, you know, rate of stenosis that was occurring, and I'm not suggesting this become part of your procedure, you're the inventor and developer of this. But I felt if you follow a timeline when you start to see stenosis formation in these children if that could be your guide as far as the

placement of a stent, you know, similar to a coronary stent, let's say. Something expansile that can open up the stenotic area. I just didn't know if there was any data looking at stent -- I'm sorry, stenosis timelines following anastomosis using this device.

DR. TED HEISE: Thank you, Dr. Dracker. This is Ted Heise for the sponsor. I think your clarification is really helpful and we will certainly be having our access to a good bit more data on the number and timing of dilatations that are necessary for stricture once we've been able to gather the PAS data from the cases above and beyond the primary outcome data that we already have. Thank you.

OPEN PUBLIC HEARING

DR. KELLY WADE: Thank you. At this time, I will open the open public hearing session. Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place

great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation. Are there any hands raised for open hearing participants? Not at this time. We will continue then with our ongoing clarifying discussion conversation.

CLARIFYING QUESTIONS

DR. KELLY WADE: Please remember to state your name before your question and please let us know which speaker you are referring to with the question. I would like to call on Dr. Sarah Hoehn for her clarifying question.

DR. SARAH HOEHN: Thank you, Dr. Wade. My name is Sarah Hoehn. I am a member of the committee. And I have a question for Drs. Zaritzky and Slater about the information that was presented by the FDA on, specifically when we talked about MDR number seven. That was the four-month-old baby that had an acquired, or potentially a tracheal esophageal fistula that was created from the magnets. And I understand both from the FDA's perspective and from Cook's perspective that the thought that all of this was from physician misuse of the device. So my questions were whether or not, from Drs. Zaritzky and Slater, if they think there should be recommendations for the labeling about who is involved in the care of these babies? In particular, whether or not there is a standard as to whether or not pediatric surgery is involved in all of the babies.

And the reason I thought about that was because of what was presented by the

FDA. It sounded like there was a new consult on four days after the procedure on, in particular, that MDR number seven which was on page 14 of our packet. So I guess my specific question for you is what are your recommendations for monitoring after placement? And what are your specific recommendations for multi-disciplinary team approach in terms of how many people you think should agree prior to placement of the catheter? I hope that makes sense.

DR. BETHANY SLATER: I'll start with that. I think that's a really great question and something that I've been thinking a lot about. I will say there is a lot of communication when a candidate for potential Flourish device placement is identified with, you know, certainly Dr. Zaritzky and the rep in regard to if the patient is a candidate looking at the esophagram. And then there is a process of training for the physician placing the magnet. It's a little hard for me to determine or answer that question as a blanket statement. I think that it's certainly something worth considering. At the very least, there certainly needs to be a training period for the physician who is placing it and make sure that they really understand what should be done and the intended use. As you rightly mention from looking at the notes from this case there definitely was some manipulation done that was not the typical intended use with the Flourish device. So I think that there should be more discussions regarding exactly, you know, who should be placing it and what type of centers it should be placed at.

DR. SARAH HOEHN: Thank you.

DR. KELLY WADE: The next question is from Randi Oster. You may need to unmute. Great.

MS. RANDI OSTER: Can you --

DR. KELLY WADE: Yes, please --

MS. RANDI OSTER: Hear me?

DR. KELLY WADE: Yes, we can hear you.

MS. RANDI OSTER: Okay, you can hear me?

DR. KELLY WADE: Please introduce yourself and state who the question is directed at.

MS. RANDI OSTER: Yes, this is Randi Oster, the consumer representative. And I don't know who has the answer, so I will leave that part open. My question has to do with the 33 cases. Do we know, was it 33 different doctors, was it two doctors? So what we are seeing, what we've been reported on is that in every case, "the physicians exceeded recommended device use and we have seen an improvement over time." My question is, is that individual learning from a physician? And so, I would like some understanding of who's doing this. And the reason for this question goes back to even the previous question. When it comes to labeling and the desire for a transparent process what do we need to tell families about the number of times a physician has done this operation? Thank you.

DR. TED HEISE: Yes, thank you for the question. This is Ted Heise for the sponsor. I'm not able to share screen. We had a slide in our presentation that I think is responsive to your question in that there were -- of the 33 patients treated they were treated in 20 hospitals. And a couple of those had more than one treating physician but they were not all -- I guess the bottom line is there were probably half a dozen physicians that have treated more than one case. We have not seen, although looking at it, a particular pattern in success, greater success in a second case than in a first case.

DR. KELLY WADE: Thank you for that. Dr. Randall, your clarifying question and who will it be directed at?

DR. RANDALL: Dr. Wade, I think -- are you referring to Dr. Flick?

DR. KELLY WADE: We can move on to Dr. Flick if you prefer. I do see your hand raised, Dr. Randall, that's why I called on you. Oh, sorry. I get it. I just had the names

transposed. I'm so sorry. Dr. Flick.

DR. RANDALL FLICK: That's okay. Thanks, Kelly. Let me just first reinforce the point made by Dr. Hoehn. I think having -- I was surprised as well to see that there was a case, or appeared to be a case, where a pediatric surgeon was not part of the care team up front and I think that's important. My question is for Mr. Heise, I believe. It could be answered by others, I think. But you state that there's a 5 percent mortality under standard care and correct me if I'm wrong but I think that's 5 percent mortality for all comers. And if that's the case -- and you also say that the mortality rate is lower with this device than with standard care but I think that's somewhat a misrepresentation. The numbers here are just simply too small to make comparisons between standard care and this device. I think if we did a calculation, we'd probably find the upper bound of the confidence interval here is probably well in excess of 10 percent mortality. Can you comment on that?

DR. TED HEISE: Yes. This is Ted Heise for the sponsor and your point is well taken. The numbers are absolutely very small and there is -- I would be very confident that there are no real statistical differences. I think we're just satisfied and comforted to know that there have not been events of death with use of this device.

DR. RANDALL FLICK: Yeah, I think -- so let me just press the point a bit. But I think we can say with confidence that we do not know whether this device is safer or less safe than standard of care. And comments beyond that we simply can't make. And so, the comments in your slide presentation are somewhat misleading when you say the mortality rate is lower. And you can go to that slide, I can't. But you say the mortality rate is lower and we just simply cannot say that and more importantly should not say that.

DR. TED HEISE: Point taken.

DR. RANDALL FLICK: Thank you.

DR. KELLY WADE: Thank you. Dr. Fischer, you have a clarifying question. Please state your name and let us know who the question is directed towards.

DR. GWENYTH FISCHER: This is Gwen Fischer. I have a clarifying question to the sponsor. Was wondering if you could offer a little bit more detail about your ongoing PAS study? It sounded like you were reverting to retrospective patients based on enrollment. Wondering if you will continue to collect prospective data as well and if the inclusion/exclusion criteria for that study will be similar to your submitted HDE studies? And then related to Dr. Flick's question, whether your PAS study will also include a comparison to the surgical open approach? Thank you.

DR. TED HEISE: Yes, thank you for the question. Ted Heise for the sponsor. We do have a -- I can provide a little more detail on the PAS plan. It does include the option for retrospective and prospective data collection. It typically is set up – it is done as an approach to the patients allowing consent to -- for their consent for the sponsor to access medical records by way of the facility. And the -- for those patients that have already completed their treatment along with -- far enough in the past, that data collection will be entirely done after the fact by going back through the medical records to collect the available evidence. For those patients who are more recently treated it will probably be -- it's a combination in that we will collect the available data at first opportunity and then at intervals we will go back to collect the additional data as it accrues. I'm not sure that was answering all of your question, so if there was a little more, please let me know.

DR. GWENYTH FISCHER: The only additional piece of that was just whether there would be a comparison to the open surgical approach?

DR. TED HEISE: Right. We have not contemplated doing that. I think there is value in considering the state of the art and the other treatment options as part of the

interpretation of the results as they're gathered in and evaluated. As previous panelists pointed out the numbers are going to be way too small to make any valid statistical comparisons.

DR. KELLY WADE: Thank you. Dr. Czaja?

DR. ANGELA CZAJA: Thank you. Angela Czaja, member of the PAC. I think this question probably is going to be directed to the sponsor. In our first question posed to the committee, because it is asking us whether the labeling changes would sufficiently address and mitigate the adverse events risk, I was wondering if you could be a little bit more explicit about what is the training involved prior to physicians using the device? Is it for all physicians? And then what are the steps in training?

DR. TED HEISE: Yes, thank you, Dr. Czaja, for the question. This is Ted Heise for the sponsor. And the training program is carried out by a seasoned product manager who has been with this technology since its inception. It goes through in a pretty detailed way not only the instructions for use but all of the warnings and precautions, including the additional warnings not to maintain -- not to lock catheters or apply excess force to the catheters. That has been done since FDA approved those changes in -- late in 2020 and I think we've had pretty good results since that was implemented. I have pretty good -- I have very good faith in the completeness of the training program. The physicians are asked to sign off that they've received and they understand the training. I think once that's happened the actual practice that the physician may apply is really, for the most part, out of the hands of the company. We don't have a lot of ability to have an influence on it.

DR. KELLY WADE: Dr. Jones.

DR. BRIDGETTE JONES: Thank you. My name is Bridgette Jones. I'm a PAC member. I have a question for the sponsor. One of the potential recommendations that we're being asked to consider today is providing additional information to the label regarding

clinical variables to better identify suitable candidates for use of the device. And so some of these variables that have been listed and some of the information provided is patient anatomy, length of pouch, location of PEG placement, fibrous tissue. So I'm wondering how were these clinical variables identified from the small number of cases? Are these kind of theoretical considerations or are there some additional data or information that helped inform identification of these variables? And just overall, do you think you have enough data to actually make these types of specific recommendations?

DR. TED HEISE: Thank you for the question, Dr. Jones. This is Ted Heise with the sponsor. And I'm going to make a brief comment and then throw it over to FDA. I think this is coming from the FDA question. We do not actually have sufficient data to be able to make recommendations on clinical variables at this point. And I'm thinking that that question may be in anticipation of having that data once we've completed the data collection through the PAS process. But FDA may wish to clarify or correct anything I got.

DR. JIAN CONNELL: This is Jian Connell from FDA. Yes, so the sponsor initially provided this information that there were additional clinical factors that could impact the magnet attraction and also the successfulness of anastomosis. So this is the list provided by the sponsor. FDA did request additional information from the sponsor. Regarding during their PAS study, that's -- the Cook promise that they're going to assess additional information regarding the clinical factor at the conclusion of their PAS study. So, FDA have a follow up question to Cook and that's what kind of information they're going to collect for their study. And we're still waiting on that information from Cook. We'll expect that information, I believe, by the end of next week.

DR. BRIDGETTE JONES: So are we being asked today to consider adding these variables to the label or are we being asked to consider obtaining further data to support

whether or not these should be added?

DR. JIAN CONNELL: Thank you, Dr. Jones. This is Jian Connell again. Yes, we want the panel to provide us some advice in this area. If we do think these variables going to have an impact on the successfulness of anastomosis we want panel to maybe provide some instruction in the collection of PAS data during Cook's study so we can take this opportunity to see what kind of additional information could be, eventually be put in the labeling if that is due to be recommended. And if not, what other things could be done. So we look forward to your comment on that.

DR. KELLY WADE: Great, thank you. Dr. Lukish. You will need to unmute. Perfect.

DR. JEFFREY LUKISH: Can you hear me now?

DR. KELLY WADE: Yes.

DR. JEFFREY LUKISH: Hello?

DR. KELLY WADE: Yes, we can hear you.

DR. JEFFREY LUKISH: I'm working on two different devices here so I don't know which one you can see me on.

DR. KELLY WADE: That's okay. We can see and hear you.

DR. JEFFREY LUKISH: So, I have several comments and one, I think, important question. Again, Jeffrey Lukish, professor of surgery and pediatric surgeon at Children's National. And I'm not sure which one of the three want to take it. And I think I said this last year, I applaud the device. I think the device is a good device. I think a lot of the complications that have occurred -- and I call stricture a complication in addition to the MDR sort of no to the other things. Most strictures will require more than stenting and surgical intervention, at least historically. So, we're really comparing two different -- and I think that

this is important for the panel to understand, I think this device is a very good device for the pure atresia with no TEF. There's no scarring, there's no anatomic disturbance that has occurred beforehand. And therefore, utilizing it in that -- in a pure atresia infant makes just very logical sense. Because that represents 7 percent of TEFs, that's about a one in 80,000 live birth anomaly pure atresias.

The more common atresia is the one that has the distal TEF. And I'm not sure how many of the cases were those cases where the TEF was ligated and then the device was introduced following ligation. I think in that patient population you run into significant issues with the deployment and migration of the magnets. Mostly because it's an uncontrolled anatomic bed and you don't know how much scarring is there, you don't know what the previous surgery has done. And so it's much, much more challenging to extrapolate the success of that instrument or the failure of the instrument in that patient population compared to the pure atresia population. All right? So you're really comparing two different patient populations for this device.

And because the pure atresia, which the device is a perfect opportunity to repair that defect, is so rare, we've kind of grouped these other ones in there to try and create a higher number so we can then determine whether it was safe, not safe, and so forth. But again, I would urge the panel to think about that, the two different patient categories where the device is used. Because it's not as simple as they're the same, they're pure atresias. One was born with it where there's no anatomic disturbance, and the other one is made a pure atresia as a result of an anatomic disturbance. And I think a lot of the MDR complications are in those kids that had a previous TEF ligation. Now, that's my comment. Now my question is -- and I think that this is important for just the pediatric surgeon that would contemplate using this for the right candidate. And that is, how do you determine -- how is the surgeon determining that gap

distance, that initial gap distance?

And I think the package labeling says it's got to be four centimeters or less. And is there specific details of how that gap length is determined? Because I know that Dr. Slater and probably Dr. Zaritzky, there is significant variability in how a surgeon deploys metal probes into the proximal and distal esophagus to determine that length. And there is tremendous variability. Some would say that you can only accurately determine gap width by thoracotomy or thoracoscopy because different pressures. And I think that that's important because if you're not starting with the right gap width then it changes how the magnets function, it changes the amount of pressure that you have to potentially apply across the anastomosis. It's just very complicated. So my question is how do we -- how are we -- and is that addressed in the labeling, that gap width? Thank you.

DR. TED HEISE: Thank you, Dr. Lukish. Ted Heise for the sponsor. Regarding the different patient populations, I suspect you're exactly right. We do plan to collect the atresia type and the nature of prior surgeries as part of the PAS and are hopeful that will help us understand how important that difference -- those different patient populations may be to success. Regarding measurement of gap length, again, spot on. We went through the same thing with the earliest commercial experience with the device where submitted imaging was, shall we say in some cases, optimistic about the gap. And it became clear that the measurement had been made with relatively rigid probes placed into the pouches likely with some tension applied on them in the interest of trying to make sure that it came in under four centimeters, if you will.

We, fairly early on, probably about the end of the first year of commercialization we added instructions in the labeling to clarify that flexible probes should be used so that there -- and not tension so that a more meaningful gap measurement was made. Clearly there is no

perfect way to measure that gap but I believe that's made some improvement. Once we have the imaging for all of the cases as well, we may be able to glean more information out of that. Thank you.

DR. KELLY WADE: Thank you. I would now like to ask if there are any speakers present for the open public hearing? We will continue on with our clarifying questions then. Dr. Havens?

DR. PETER HAVENS: Thank you. Peter Havens, a member of the PAC. I have two questions. One goes, I think, both to FDA and to the sponsor. The question is, can you make use of the device contingent upon enrollment in the PAS?

DR. TED HEISE: Ted Heise for the sponsor. I don't believe that's an option, practical option at least. Certainly, the company doesn't have the authority to do that that I'm aware of.

DR. PETER HAVENS: So then the question could go to the FDA. Does the FDA have the ability to do that since so much of what we're talking about is how to ensure we have adequate data to make further decisions, enrollment in the PAS becomes a critical issue.

DR. LAUREN MIN: This is Lauren Min from FDA. I believe that in this case Cook presented earlier today that they have 33 patients who have been treated since HDE approval. And of those, FDA is aware of six patients, and they're updated that to nine patients who've been enrolled in the PAS so far. I believe that an attempt to enroll more of those patients who have already been treated and following them up to two years post Flourish treatment or study exit, that would be the best approach to getting these data in a more timely manner. Currently there is not an enforcement in place to require PAS enrollment as a condition for receiving Flourish treatment.

DR. PETER HAVENS: But you could do that? That's my question.

DR. LAUREN MIN: That I would defer to one of my FDA colleagues.

DR. PETER HAVENS: Hearing no FDA colleague willing to take that question.

DR. VASUM PEIRIS: This is Vasum Peiris, can you hear me?

DR. PETER HAVENS: Yes, thank you.

DR. VASUM PEIRIS: Hi, Peter. How are you?

DR. PETER HAVENS: Good.

DR. VASUM PEIRIS: Thank you, Lauren, for the follow up there. The simple point here, Peter, I think it's a very -- it seems like a simple answer, right, that you're suggesting and a very reasonable one as well. Especially when we consider the issues with respect to data collections in these small populations. I'll try to keep this point simple. But generally, after a device has been approved, as this device has, to the HDE pathway use of the device is not contingent on enrollment in a study. So the simple answer to your question is no, we don't do that.

DR. PETER HAVENS: Usually you don't. Do you have the authority to do it? That's the question.

DR. VASUM PEIRIS: No. Once a device is approved for market in the United States the device is available for use under -- generally under the labeling requirements, but up to the physicians and the patients that can decide how to most effectively use that device for their needs.

DR. PETER HAVENS: Thank you. The next question is -- concerns what many people have gotten to which is this is a rare disease, use of the device is equally rare and so for most people using it, it's the first time they would use it. And I appreciate the sponsor's statements that they have training in place but it also seems clear that in spite of the training people have not been using it the right way. So is there a way that the Cook team can have

ongoing input into the use of the device?

DR. TED HEISE: Thank you, doctor. Ted Heise for the sponsor. One comment to your question about requiring participation in the PAS. There's generally a fairly protracted contracting process required to get everything in place to allow that. And these cases are not often -- they're not emergency but there's an urgency involved so that complicates the process somewhat. Regarding the training and its effectiveness. I just want to maybe expand a little bit on the discussion that's been presented already by pointing out that the perforation and the potential perforation happened before the labeling improvements and strengthening of the warnings were added and implemented -- approved, added, and implemented. The one case that has happened since then, specifically the perforation TEF, was actually a case in which the physician was relatively strong willed I guess I should say and in fact has lost privileges at that hospital since then. So I think that's a case that was somewhat unusual for those reasons.

DR. PETER HAVENS: Okay. Let me -- thank you very much for that answer. Let me get back to the PAS question because it's a central -- you could make a central IRB that would have the ability to make this happen. This is a crucial issue to think about not just in this device but in other areas where post-licensure data collection becomes a critical issue. And as the sponsor pointed out this takes a lot of time at a site. So if you can centralize the IRB and make that work, that's a way to get the data for everybody who's using it. And you would -- Cook could do that. There are plenty of central IRB approaches that the FDA could, well, I think, do more to demand. But that's a different -- that's just me. I'll stop now.

DR. TED HEISE: Thank you, Dr. Havens. I completely agree. And I may not have made it very clear in the presentation, but the company has in fact established a central IRB for the PAS. The difficulty comes in that many hospitals are not willing to operate under that approval and need to run it through their own processes for whatever local reasons and

considerations they may have.

DR. PETER HAVENS: Right, I understand. Thank you.

DR. VASUM PEIRIS: Peter, this is Vasum again with the FDA. Just wanted to add a little bit to your points about the IRB process. The FDA has recently released some guidance clarifying information regarding how HDE devices can be authorized via a central IRB. Other reporting requirements still exist with respect to each use of a device and there's variation with respect to emergency use that can be provided to the IRB or the local coordinating committee after its use. But we've provided that guidance to help clarify and facilitate uses of these devices for patients that need them and also to help clarify a bit more about the point that these devices are not experimental devices, these are fully marketed devices despite the reception of humanitarian use device or the humanitarian device exemption.

DR. PETER HAVENS: Thank you, very much, for that clarification.

DR. VASUM PEIRIS: Thanks, Peter.

DR. KELLY WADE: This is Kelly Wade. On this exact same topic, Mr. Heise, I wonder if you could clarify. For the patients with the MDRs that we reviewed today have you exhausted all efforts to get them in the -- sorry, just getting my camera on. Have you exhausted all efforts to get those infants of the MDR reports to enroll in the post-marketing study? Or are you still trying to get some of those patients involved in the retrospective post-marketing study?

DR. TED HEISE: Dr. Wade, thank you for the question. Ted Heise for the sponsor. As you might expect, some of these situations, the hospitals are not always that eager to talk to us about cases that have had problems. We are doing our best. The one particular case with the TEF was actually treated at three different facilities. The second one, because of the need for pediatric ENT service, they did have surgery at the first site but they felt the bronchoscopy was needed which they could not do. We have not exhausted all of our options

yet. We are committed to continuing to pursue this with every case recognizing that in the end we may not succeed with all of them.

DR. KELLY WADE: Thank you. I think that's an important feedback. I will now call on Dr. Sayej for a clarifying question. And remember to state your name and who the question is directed to.

DR. WAEL SAYEJ: Thank you, Dr. Wade. Hi, this is Dr. Wael Sayej, pediatric GI from Bay City Children's. I am a PAC member. A couple of questions, small questions and a comment. Number one, the low enrollment numbers are not surprising given how rare this disease is. Especially the isolated esophageal atresia. However, my question is, how many centers are actually involved? Are the large pediatric children's hospital centers involved in these studies or not? And is there something that is also being expanded beyond North America or is this just limited to North America right now? Number two, Dr. Havens took the words out of my mouth with regards to training. I understand there's training, but is there any way to have a team of oversight to guide the physicians who are involved in these procedures and to really ensure that they don't deviate from what these devices are intended for?

And in response to Dr. Flick, I agree with you that we can't say that the mortality rate is lower since we don't have enough data. However, we do know that there have been no mortality rates which is very reassuring -- or no mortalities with this device, which is reassuring. However, that doesn't mean that there won't be any. We have to be prepared to really be aggressive with treating these patients if they develop any perforation or anastomotic leaks since they can lead to really devastating outcomes. My last comment is regarding strictures and stents. I, three or four years ago, was involved in translational research on doing esophageal implants for the purpose of treating esophageal atresia and we used a biliary stent for infant piglets and we used esophageal stents for larger animals.

At the time of placing the implants and after the strictures were placed two of the big problems that we saw were stent migration was very common and it was not unusual for me to go in and put in stents every week in these animals. And number two, even with the stents, the risk of strictures was not any better. So I just want to keep that in people's mind that I think this is a disorder, unfortunately, where strictures will develop regardless of whether this was performed with a thoracotomy, thoracostomy, or use of the device.

DR. TED HEISE: Thank you, Dr. Sayej, for the comment and the questions. We do have nine sites with IRB approval for the PAS and those are all in the U.S. We have proactively gone to larger children's hospitals. Obviously, it's hard to predict where these cases are going to show up. It's a considerable undertaking to pursue every children's hospital in the U.S. on the chance that they might get a case. We are also in the process of application to Health Canada for paperwork and permission necessary to do data collection in that country for those cases. It's a little complicated because those were carried out under special access provisions, so we can't just go in and ask for the data, we have to get an actual authorization to do that from Health Canada. Regarding the support for the case, we do have our experienced product manager who is in attendance at every case and he is there for the placement and the training.

Obviously, these patients are set with -- they sit with the catheters in place for a number of days, often even up to a couple of weeks. And it's just not practical to have a company representative live at the hospital for that length of time.

DR. WAEL SAYEJ: Just one additional question. These babies, I mean, I understand these catheters can stay in place anywhere from three days up to two weeks. Are they being fed through the feeding port of the tubes or are they on TPN? And if they are on TPN, I'm assuming they require a central line, right?

DR. TED HEISE: I think it's a mix. I don't think we have all of that data yet. I do know that the G-tube component of the Flourish device is used in some cases for feeding.

DR. WAEL SAYEJ: Thank you.

DR. KELLY WADE: Thank you. The next clarifying question, I will call on Dr. Flick.

DR. RANDALL FLICK: Thanks, Dr. Wade. Randall Flick, PAC member. So I just want to expand a little bit on the comments of -- what I think were excellent comments by Dr. Lukish. So TEF is a -- has a very broad range of presentations and outcomes are often driven by comorbidities as much as they are by the pathology itself. And as we -- at least as I review the materials, I find that we're comparing children treated with the device versus all other patients, all kids with TEF, which makes comparisons very difficult. And in designing the PAS I just wonder why we don't have a set of controls, historical controls, that are matched for things like the type of TEF, the birth weight, presence or absence of pulmonary disease, or cardiac disease. These are the things that drive outcomes and these are the things that will often help us better understand whether this device is actually better than standard care. So I'm not sure who's best to comment on that. Maybe Dr. Min or Dr. Peiris or the sponsor.

DR. TED HEISE: Well, Ted Heise for the sponsor. Thank you for the question. I don't have a complete answer for the question. I guess I would submit that the availability of the comparator data that you suggested, particularly for mass case type of analysis is probably not great. There isn't, as you know, a lot of patients that are treated this way and trying to gather that data would probably be quite a challenge. I don't know.

DR. RANDALL FLICK: Well, they don't have to be concurrent controls, they could be historical controls. And each of the centers almost certainly have historical patients that they could use as a comparator. But Dr. Min or Dr. Peiris?

DR. LAUREN MIN: This is Lauren Min from FDA. I would just add that when we worked with Cook to design the post-approval study it wasn't -- we didn't have questions about the effectiveness. It was mainly to assess safety. And based on the pre-market data we wanted in particular to know about stricture rates. The other piece that I would add is, usually when we think of devices where we want historical controls, we look to existing registries where -- to provide that data. And in this case, we're not aware of an existing registry where we could pull appropriate controls for a comparison.

DR. RANDALL FLICK: Yeah. It just occurs to me that University of Chicago certainly has a long history of taking care of patients like this. The information that is most relevant are very easily obtained from historical controls. Birth weight, presence or absence of heart disease, et cetera, would make it far easier to make comparisons of both outcome and adverse events or complications. So I'll stop beating the dead horse, I guess.

DR. VASUM PEIRIS: Randall, this is Vasum. Just to add a little bit to what Lauren mentioned as well. Again, very insightful and relevant comments that you're making. As you fully likely recognize there are distinctions with respect to the FDA's process with respect to developing post-approval studies. The focus here is that pre-market, post-market balance with respect to the data that we believe is appropriate to continue to monitor safety issues and concerns. And to be able to address distinctions between how a device may perform in a clinical, regulated trial setting prior to marketing approval. Versus in the post-market setting that may have a little bit more variability certainly with respect to operators, conditions, and even areas of the country and different types of settings and devices used.

To your point about the clinical management issues, and I think it's a really important one, there isn't any problem with respect to utilizing data that we collect in the PAS to be subsequently compared with other clinical data that may be historical controls. That

certainly is an option that is available to the broader community. The data that we collect is also available to the broader community. Your teams and other investigators can certainly consider that. It's not part of our specific designs in the post-approval studies.

DR. RANDALL FLICK: Thanks, Vasum.

DR. VASUM PEIRIS: Thank you.

DR. KELLY WADE: Thank you. Dr. Lukish, your hand is still raised. I'm not sure if that's another question or -- okay. I see your hand taken down. Thank you. Randi Oster, you have a clarifying question?

DR. PETER HAVENS: Randi, you're muted. We're not hearing you.

MS. RANDI OSTER: Can you hear me now?

DR. KELLY WADE: We can hear you --

MS. RANDI OSTER: Hello?

DR. KELLY WADE: And see you, Randi.

DR. RANDALL FLICK: Yes.

MS. RANDI OSTER: Yes? Okay. I have a clarifying question building on what Dr. Lukish and Dr. Flick have been talking about and my question is to the sponsor. And the question is, do they have the data segregated for the pure cases versus the other cases? And is that made available in the training so that a physician can understand the likelihood of complications and therefore, perhaps advise the family about outcomes as well?

DR. TED HEISE: Ted Heise for the sponsor. Thank you for the question, Randi Oster. We do not have the atresia type for any of the non-PAS cases, that's the majority of the patients that have been treated. That is one of the variables that will be collected as we move those cases into the PAS data collection. So our goal is to collect the type of atresia that was treated so that we can use that to hep understand the impact of that covariant or that patient

characteristic on outcomes.

DR. KELLY WADE: Thank you. I will ask one more time if there are anyone -- any speakers present for the open public hearing which will conclude at 12:30. I see that there are no hands raised. I'd like to really thank the members of the FDA and the sponsor. I'm sorry, Randi, did you have something to say before I conclude this morning's session?

MS. RANDI OSTER: No.

DR. KELLY WADE: Okay. Sorry, you popped up on my screen so I just wanted to be careful. I really want to thank the members of the PAC, the sponsors, and the FDA for this robust discussion this morning. I think I would conclude by really summarizing that TEF is a serious congenital anomaly among infants, a small subset of whom are eligible for the use of the Flourish device. The comments and clarifying questions from the PAC this morning have focused on the importance of enrollment in the PAS study for more comprehensive data about these cases, specifically to make sure that we are enrolling patients in the post-marketing study that have had these complications or adverse events that we reviewed today. There was also attention drawn to the importance of patient selection for device use and important consideration for a comparable group of historical controls with these specific defects, both the type A and type C of tracheoesophageal fistula. So really the importance of having a similar comparator group of infants for comparison.

And finally, the committee highlighted the importance of physician training in the use of this device. It is now close to 12:30, 12:28, and with no further comments of open public hearing speakers I'd like to call the open public hearing to a close. We will adjourn for a 30-minute lunch break. We can keep this -- yep, great, we can adjourn for a 30-minute lunch break and we will resume the meeting at 1:00. I'd like to remind members that there should be no communication of the meeting topic during the break amongst yourselves or with any member

of the audience. And again, we will resume at 1:00 eastern standard time for further discussion and voting on the three clarifying questions put before us.

[LUNCH BREAK]

COMMITTEE DISCUSSION AND VOTE

DR. KELLY WADE: It's Kelly Wade. I'd like to welcome everyone back from lunch. We can now proceed with the meeting. Please raise your hand if there are any other clarifying discussions or questions for the FDA or panelists. If not, given our robust discussion this morning, we will proceed with looking at question one. Great. Question one is being shown on your screen. It states, "Recurrent and improper use of the device was observed in the new serious adverse events. Also, the attractive force of the magnet increases as the distance is reduced. Does the committee agree that additional warnings about improper device use, including excess user manipulations of the device and an explanation of the magnet behavior would address and mitigate the risk of perforations or TEF?"

Are there any questions or comments specifically regarding the wording of the question? Put your hand down if it is not specifically about the wording of the question. After that, we will then proceed with further discussion. The first set of questions is only in regard to the wording of the question. Again, this is not an open conversation of discussion about this question but simply the wording. I will start with Randi Oster.

MS. RANDI OSTER: Yes. Can you hear me? Hello?

DR. KELLY WADE: Yes.

MS. RANDI OSTER: Can you hear me?

DR. KELLY WADE: Yes.

MS. RANDI OSTER: My specific question is, if we wanted to add additional provisions in this question to answer yes, is that an opportunity? Or are these the only things, warnings, the user manipulations, that you can address? Because the add mitigates the risk. There are other risks that are not addressed in this question. Therefore, the follow-up to that is, then if we vote no, does that mean that even these things that are identified we don't think are needed? How do you have the questions if we believe there were additional things that should be in the sub vote there?

MS. JIAN CONNELL: Jian Connell from FDA. Thank you for your question. Yes, currently this question is only specifically towards the four cases we reported to the PAC this year, including the perforation cases and the TEF case. FDA have continued doing the post-market surveillance. That's including the MDR information, post-approval data and the literature reviews. If at any time there are any new risks or new issues arise, FDA going to reevaluate the information at that time.

MS. RANDI OSTER: Just as a follow-up, then if we vote no, what would the FDA interpret that as?

MS. JIAN CONNELL: That would represent your opinion, and we will consider that. Thank you.

DR. KELLY WADE: Bridgette Jones, is your question referring specifically to the wording? Go ahead.

DR. BRIDGETTE JONES: Yes. Bridgette Jones, PAC member. I was

wondering can the FDA provide any other specifics in regard to what is meant by "additional warnings?" Does that mean adding specific warnings to the label or specific types of warnings? Can further clarification be provided on what "warnings" mean here?

MS. JIAN CONNELL: Jian Connell from FDA. Thank you for your question. Yes, this additional warning regards to additional warnings after that 2020-approved HDE supplement which Cook submitted to FDA regarding especially for perforation cases. This additional one would be specific, warning the physician to not apply sustained force to the catheter in an effort to improve the magnet advancement. That may increase the risk of subsequent perforation or TEF. We also want to clarify some information about how to reposition the device after the Flourish device placement. That would be when the catheter is not at a specific position that we recommending. This way, any clarification would be avoiding some unnecessary adjustment of the device and to facilitate more success of the anastomosis achievement.

DR. BRIDGETTE JONES: Okay. Just to follow-up on that, if those additional warnings are added, would that just be simply added to the label? How is that going to be communicated to clinicians or surgeons or potential users?

MS. JIAN CONNELL: FDA proposed to Cook including in the direction for use and also in the physician training so that way everybody will be updated on the information. In the training, the physician will acknowledge that they received this information. FDA would also consider in their Cook representative training maybe -- considering with this new revised labeling, maybe they should do a retraining of their representative before they train the physicians.

DR. BRIDGETTE JONES: Okay. Then, I have one more question about this question. It says with additional warnings and explanation of the magnet behavior that it would address and mitigate the risk of perforation or TEFs. "Would" to me sounds like a pretty strong word here. Is there a reason why that word was used instead of "may address or mitigate risk" because I'm thinking there's additional risk factors here other than what this additional warning would address?

MS. JIAN CONNELL: Thank you for that suggestion. Yes, we will consider that. Thank you for that suggestion.

DR. KELLY WADE: Great. Given the number of hands raised, I'd like to just add one comment, that as we proceed with questions and open the question for discussion, I would like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Next, I will call on Dr. Hoehn.

DR. SARAH HOEHN: Sarah Hoehn, Pediatric Advisory Committee. This is a follow-up to what Bridgette and Randi were just asking about. I think we have a shared concern that the language of the question about the additional warnings of improper device use, everything after that comma, none of it addresses the physician behavior piece. I do appreciate what was said about perhaps retraining the Cook representatives to retrain the physicians. I think if there could be anything added to the warnings about ensuring that there is a multidisciplinary team that agrees that this an appropriate use, especially given what we heard about the variability. Then, anything that addresses the issues of physician behavior and making sure that there's appropriate patient choice because all the perforations were related to that. That's not addressed in

the current wording of the language after "additional warnings."

MS. JIAN CONNELL: Thank you for your question. We considered a multidisciplinary team as a standard of care. We'll consider that to be already included in the regular practice and not specifically only related with this device. That's why it's not included in here.

DR. SARAH HOEHN: Thank you.

DR. KELLY WADE: Angela Czaja.

DR. ANGELA CZAJA: Thank you. Angela Czaja, member of the PAC. I had some similar concerns about the wording used in terms of "would address" and "mitigate the risk" because I'm not quite sure how I should answer that. Do I think there should be some additional warnings included, especially along with additional training? Yes. Do I think that this would address that risk entirely? I'm not sure that that I could answer completely yes. I'm wondering, along with some of the other comments, as this specific word choice sounding a little bit too strong and definitive for me to feel completely comfortable answering yes to the entirety of the question.

MS. JIAN CONNELL: Thank you for your questions. Yes, it's a similar like my answer to earlier. Yes, we would, specifically regarding the causes related to the manipulation of the device. With that into the context, we think hopefully this would address the mitigation risk. But if the panel feel there's some other areas we should also look at, hasn't discussed, other than the training or in other places, this is currently the thing we considered as the best to the patient's safety and benefit. There will always be some risks arise, unexpected risks coming up, no matter to device or drugs, that would be some unexpected, not happened in the preapproval clinical status, that is happening.

That's why FDA has this post-marketing surveillance program in place, so we'll continue observing and monitor these devices. And at any time there is a new safety signals arise, the FDA will promptly address those issues.

DR. ANGELA CZAJA: Thank you.

DR. KELLY WADE: I would also add -- it's Kelly Wade -- Dr. Czaja, that after we vote and state our votes, after the collection of votes, there is an opportunity to state any reasoning behind your vote into the formal record.

MS. JIAN CONNELL: Thank you. We would appreciate that.

DR. KELLY WADE: I will now call on Dr. Portman.

DR. RONALD PORTMAN: Thank you, Kelly. Ron Portman, PAC member, industry nonvoting. The last part of the question explaining the magnet's behavior and how the education would help mitigate is clear to me. What is not clear is what is improper device use. Who determines it's improper? And excess user manipulation, what does that mean? How was that determined? If that's done by training, then is that training approved by FDA? On the drug side, we would call this a REM. Will there be very specific determination of what improper or excess is?

MS. JIAN CONNELL: Thank you for your question. Improper use of the device is any use of device that against the instruction for use. Yes, training is part of the labeling that would be approved with the device labeling as part of it. Some examples of improper use specifically to this Flourish device including leaving the gastric tube in the lower esophageal pouch, which is not recommended by the labeling, or applying an additional force to try to bring the two magnets together. That's in addition to the magnet force or adding additional tension to the esophageal pouches,

which could predispose the esophageal pouches to some subsequent perforation. For these reasons we wanted to better inform the physician regarding this device and manipulation.

DR. RONALD PORTMAN: Thank you.

DR. KELLY WADE: I will next call on Richard Holubkov.

DR. RICHARD HOLUBKOV: I'm just chiming in. Good discussion. Obviously, I'm not a clinician or even a physicist. I can support this wording. Obviously, as training would address the risk, I don't know if it's affected if the warnings aren't heeded and if it's well explained. Again as a non-clinician I found the examples of the improper use, how there was a guide wire used and obviously the excess manipulations in general -- I think examples in the training and even specific examples of improper use might be helpful. That's all I have to say. Thanks.

MS. JIAN CONNELL: Thank you for your question. Mitigation means to prevent some risk or consequences from happening if we already know there is such risk. In this case, if we know when the altered use of device could most probably cause the cases happening in this perforation and TEF cases, it would have something in place to prevent this from recurring. That means we're going to advice the physicians during the training that improper use of the device could cause this risk to the patients to better inform the patient to make a good clinical decision when they are interacting with the patient during the procedure.

DR. RICHARD HOLUBKOV: Thank you.

DR. KELLY WADE: Thank you for those specific questions and comments concerning the wording of question one. We will now proceed with the

question and open the question for further discussion. I again remind public observers that, while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Are there further comments or clarifying questions or discussions? Please, members of the PAC raise your hand if you would like to further this conversation. Dr. Havens.

DR. PETER HAVENS: Thank you very much. I think that all of the questions that we've heard would suggest that perhaps this additional warnings might be a necessary first step but inadequate to fully mitigate or modify the risk of perforations and so might require these things as a first step towards a broader program to truly mitigate the risks.

DR. KELLY WADE: Thank you for that comment. Are there further comments or questions or discussion requested by members of the PAC? Dr Flick.

DR. RANDALL FLICK: Randall Flick, PAC member. Is this an appropriate place to recommend or is it possible for FDA to recommend involvement of a qualified pediatric surgeon in the care of the patient?

MS. JIAN CONNELL: Thank you for that question. Yes, regarding the physician's qualification, I think early responses I'd already addressed that. Every physician has to be trained. Every pediatrician surgeon has to be trained in order to do this kind of procedure and apply the Flourish device. Every physician will sign acknowledgment signature after they receive the training to make sure they fully understand the device use. With this improved labeling and improved physician training, we hope this would help physician to better inform them of some of the risks associated with the device so they would make a better clinical judgement.

DR. RANDALL FLICK: I know you can't prescribe what physicians use this, but I think we're not addressing the central question. Let's say, for example, a pediatric gastroenterologist decides to perform this procedure without informing or engaging a pediatric surgeon. The complications, especially the severe complications, that are going to occur are going to have to be dealt with by a pediatric surgeon. The engagement of a pediatric surgeon upfront, I know you can't require that. It might be wise to encourage that. I hope that makes sense.

MS. JIAN CONNELL: Yes. Thank you. Yes, absolutely that makes sense. We take every physician and their qualifications seriously. We believe if a physician agreed to place a device, this must be within their area practice realm. With the appropriate training, we believe the physician can do the job. Before this device can be available, I believe the sponsor side, they always receive a request regarding which hospital going to need this kind of device.

Then the sponsor supposed to provide a training to that physician after they signed an attestation indicating that they already received the training then that the device going to be shipped to them and be used. I have confidence that physicians are not going to place this device if they're not comfortable or not in their competent area. Maybe I could ask the PAC members to provide some of those feedbacks; is any physicians, if not in their practice area, will they be still doing this kind of device placement?

DR. RANDALL FLICK: Thank you. I'll let others comment.

DR. KELLY WADE: Kelly Wade. I'm wondering if it would be acceptable for us to relate this question to the sponsor team about where the involvement

of a pediatric surgeon is from the side of the sponsor in obtaining access to the device.

MS. JIAN CONNELL: Thank you for that suggestion.

DR. KELLY WADE: We've heard about a program manager. Go ahead.

MS. JIAN CONNELL: Sorry, Dr. Wade. Thank you for the suggestion. Yes, we will defer to the Cook side to hear their insight.

DR. TED HEISE: Yes, thank you for the question Dr. Wade. This is Ted Heise with the sponsor. I think it's a challenging area for the company as well as for FDA given that neither of us have a role in the practice of medicine. Certainly, we are most interested in responsible and appropriate use of our device. I think we can certainly make recommendations about additional care considerations that may need to be available for dealing with adverse events. I would maybe make the point that our latest case with the TEF was in fact performed under the care of a pediatric surgeon.

DR. RANDALL FLICK: If I may follow-up just a little bit. I just want to make sure that I'm clear here. This is a question I think not necessarily for the sponsor as for the FDA. Do we want language in the labeling that specifically strongly encourages the involvement of a pediatric surgeon. Certainly, pediatric surgeons have complications just like everyone else. In the case of the perforations or fistulas, those complications must be dealt with by a pediatric surgeon. So, their engagement upfront I think is important, and their understanding of the anatomy I think is going to be important too. Language that would encourage that training for the sponsor, that would encourage that, I think would be to the benefit of the patient.

DR. SHANI HAUGEN: Hi. This is Shani Haugen from FDA.

DR. VASUM PEIRIS: Go ahead, Shani.

DR. SHANI HAUGEN: Thank you. I wanted to add that, per the HDE approval letter, the labeling must, actually, specify the specific training or experience that practitioners need in order to use the device. While we wouldn't expect that the labeling could specify any particular board-certified physician, we would expect that the labeling would identify the experience that's needed. If there is a particular experience that is needed in order to safely use the Flourish device, then we would welcome the PAC's input on what that specific experience should be.

DR. RANDALL FLICK: Maybe what's needed is a language that ensures that the capability to deal with any foreseeable complications exists within the care team. Vasum, does that make sense?

DR. VASUM PEIRIS: Yeah. Thank you, Randall. Let me just say that I completely appreciate and understand, I think, what you're getting at with respect to your question. Allow me to provide a little bit more context and clarity here, as well, with respect to distinctions perhaps between and HDE and an approved PMA. Part of the HDE process is that overall IRB review and the potential for a local committee of experts at either the institution or whatever the institution defers to as a local committee of experts that understand the use of these types of devices, that they be involved in helping to oversee the use of these devices, HDEs and in general. There is a little bit of preexisting process that is there already for an HDE.

As been pointed out before as well, we specifically don't regulate the practice of medicine, but I think suggestions like you're bringing up, Randall, are certainly very relevant and insightful and helpful and should be considered by any of the institutions that are using this device. I just want to follow-up, and I apologize for this,

that I hadn't done this previously. I believe I am obligated also to ensure that folks know I am a fellow of the American Academy of Pediatrics. I am a fellow of the American College of Cardiology, and I'm a fellow of the American Society of Echocardiography. In addition to that, I am an attending physician at Children's National Hospital here in the D.C. area and am also an adjunct full professor at George Washington University. Randall, happy to address that further if my answer wasn't sufficient or we haven't answered as a group your question sufficiently.

DR. RANDALL FLICK: No. Vasum, I appreciate that nuance. I think we can just let others weigh in if they think it's important.

DR. VASUM PEIRIS: Yes. Thank you.

DR. KELLY WADE: It's Kelly Wade. I'd like to ask Dr. Lukish, a pediatric surgeon on the PAC today, if he could answer one of the questions posed about if anyone other than pediatric surgeons is using these devices at this time. Is it moving into the realm of interventional radiology or general surgeons for patients of all ages? Is this currently restricted under the use of pediatric surgeons? Could you answer that, Dr. Lukish? He may be offline right now, so I'll come back to him. There's a hand raised by Randi Oster.

MS. RANDI OSTER: Yes. I want to determine if we could add in some language that we discussed this morning. The recurrent improper use of this device, we had discussed this morning, there were two key areas. One was the type of patient; was it a pure patient? The other one was the experience of the doctors. In both cases, the sponsor did not have the data segregated. Therefore, I'm wondering can the question be "Does the committee agree that additional warning about," and then we would include

the patient's comorbidities as one of the things that you need to look at as well as the level of experience of the doctor and add that into the commas so that it could be a yes vote? Otherwise, if it's a no vote, I would still want those things considered.

MS. JIAN CONNELL: Vasum, you want to take that question?

DR. VASUM PEIRIS: Sure, Jian. Thank you. Randi, I think again, bringing up some very relevant and important points here in front of the overall conversation that we're all trying to address. With respect to this question itself, I'd suggest that we consider the question in its focused area, and we can certainly consider all the other points that the members of the PAC have brought up for thought here. Just to be a little bit more clear perhaps, as I've mentioned before, the FDA does not regulate the practice of medicine. There are basic standards across the board, across the country, with respect to how medicine's practiced and the regulations of medicine.

Each state medical board has its own authorities in terms of providing licensing, ensuring continued CMEs for all physicians and continued licensing for those physicians, and each hospital has its own process by which authority is provided to physicians to practice in different areas. For instance, as I mentioned earlier, I am an attending physician at Children's National. My clinical boards are in pediatrics and pediatric cardiology by the American Board of Pediatrics. And, I'm also boarded in adult congenital cardiology by the American Board of Internal Medicine. Those types of qualifications and training and experience are considered by every institution prior to allowing physicians to take on certain patients, certain acuity levels, certain techniques, consulting and procedures within a hospital.

MS. RANDI OSTER: Thank you. I just want to follow-up as the

consumer representative and a mother who's had sons who've had multiple operations, if I had a child that had an adverse reaction, and if after the fact I discovered that, gee, my child had these comorbidities which increased his risk, which is what the question's about, and I wasn't told that, which is where we're trying to get at with this question, or that there has been data, a little bit of data, but this is a training issue and my doctor happens to be his first time, the patient's family would look back at what we voted on and say, "How did you not include these things?" That's the reason that I'm pushing the issue at this time, taking it from the families that I represent to the United States and how they'll look at this in hindsight if there was an adverse event.

DR. VASUM PEIRIS: Randi, I think you bring up some extremely important questions. There is no doubt about that. I believe that all of my clinical colleagues, especially those that are in high acuity services and interventional services and surgical services, take those issues into consideration every time that they take care of a child with the patient and family. I certainly can speak for myself and say that I do, and I believe in all of my colleagues that do the same. The difference here, the distinction that may be of value in this conversation, is the role of the FDA and the labeling aspects that we're discussing versus those other very important points that you're bringing up.

That's why I wanted to be clear about what each institution is able to do, what each hospital is able to do, what each state medical board is able to do, and then fundamentally what the role of the FDA is in this aspect as well. Our approach and within our authorities we certainly want to optimize the labeling to provide the information that can provide every user, patient, physician with the information that can

allow the most optimal use of the device and safest use of the device for the needs of that patient. Those other points that you brought up, again I'll just say, I personally absolutely encourage and, from an agency standpoint, we certainly support.

DR. KELLY WADE: Thank you for sharing those points. It's Kelly Wade. We have solved some technical issues in the background. So I'd like to go back and call on Dr. Lukish, pediatric surgeon and temporary member of the PAC, for this discussion to share any insight with the committee about discussion of pediatric surgeons and whether or not the device is being used outside that specific scope.

DR. JEFFREY LUKISH: Good afternoon. Can everybody here me and see me now? Hello?

DR. KELLY WADE: I can hear you. I can't see you currently. Oh, there you go. You're all set.

DR. JEFFREY LUKISH: I'm using two different instruments. First of all, to get to the piece about training and the utilization of this device, this is a very rare, 1-in-5,000 live birth anomaly. The pure atresia is a 1-in-80,000 live birth anomaly. Very few people are going to have robust training in the deployment of the device. It is important to have the labeling as accurate and as clear as possible. That is important. I believe I would say to the panel that that is probably the most important role here, to ensure that the warnings are properly and clearly written so the interventional radiologist and pediatric surgeon are capable of deploying the device safely. I think I had heard from Ted Heise that a Cook representative comes to the hospital to assist with that whole piece. Now, most of the time when these kids are born, they're at a large children's hospital, and most of these children's care is really managed in a multidisciplinary

fashion.

Really, envisioning the deployment of this device at any of our children's hospitals in America, or Canada for that matter, is going to be carried out in a multidisciplinary fashion whereas there's not going to be one person that is solely in charge. I think that the people that are primarily involved in the care and deployment of this are going to be the pediatric surgeon and then the interventional radiologist. I can't envision doing it without assistance from both and following the child as the magnets deploy and migrate towards one another. I'm not sure that helps to answer your question, but that's my thoughts on it.

DR. KELLY WADE: I appreciate that. I think it is helpful to have your expertise. Thank you. As we wrap up before voting, I'll call on Dr. Havens.

DR. PETER HAVENS: Thank you very much. Can I clarify? This still is a humanitarian-use device, HUD. Is that right?

MS. JIAN CONNELL: That's correct.

DR. PETER HAVENS: It's approved through an HDE. Is that correct?

MS. JIAN CONNELL: Yes, Dr. Havens.

DR. PETER HAVENS: As I look on the FDA website, I quote, "An approved HDE authorizes marketing of the HUD. However, an HUD may only be used after IRB approval has been obtained for the use of the device for the FDA approved indication." Every time this device is used, it should have been presented in front of a hospital IRB. That's what it says on the website.

DR. VASUM PEIRIS: Peter, this is Vasum. Go ahead, sorry.

DR. JEFFREY LUKISH: I believe that that is accurate. I think that that

whole IRB piece, which is key -- I believe that that is one of the limiting factors in the more widespread use of this because you have to go through the IRB, which is the right thing to do so they can review all of this and ensure that it's carried out by the right personnel at that hospital. All of these HDEs, you have to get approval at your respective institution before you utilize them.

DR. VASUM PEIRIS: Yes, to add to that -- this is Vasum Peiris again -- the other option is an appropriate local committee of experts that is upheld and consistent within the institution the device is being used at. If there are emergency uses, the device can be utilized and then reported back to that appropriate local committee and/or to the IRB.

DR. PETER HAVENS: Okay. Thank you.

DR. KELLY WADE: Kelly Wade. Thank you for that clarification. On that note, I'll direct this question to Vasum. If the IRBs are already involved, then is it too much of a stretch to ask or consider a registry for these kids or the ongoing collection of outcome data for these interventions since there already is a step at the IRB?

DR. VASUM PEIRIS: It's a very good question, Kelly. There are pros and cons, certainly, to any of those types of additional steps. It's not to say that a registry can't be utilized. The issue comes up for the purposes of marketing and continued monitoring of safety from the agency's perspective. Is a registry necessary or not, and will it be helpful? Who will be managing that registry, putting it together, maintaining its infrastructure, taking care of the costs, and who would be responsible? All of those factors still need to be considered as well. You may be getting at the point

that, which I'm hoping everybody understands, since these HDEs again are under the supervision of the IRB or the appropriate local committee, that is an additional step of, I'll just say, safety review that will hopefully continue to ensure that HDEs are used appropriately by those individuals who have the training and capabilities to use the device appropriately and also hopefully are selecting the right patients that would benefit most from the device.

DR. KELLY WADE: Thank you. That was very helpful. It's Kelly Wade. As we move towards voting, I would ask someone from the FDA to clarify what is meant by "abstain." How does abstain get interpreted if there's any specific guidance you could offer?

DR. VASUM PEIRIS: Kelly, this is Vasum. The abstention option is part of the process here for the PAC certainly for a number of different reasons. Individuals may feel like they would like to abstain, and that could be a lack of clarity with respect to the question, issues around conflicts, lack of understanding to be able to answer the question sufficiently. That option exists. If abstention is selected, we will have to take the remainder of the vote into consideration.

DR. KELLY WADE: Thank you.

DR. VASUM PEIRIS: Thank you.

DR. KELLY WADE: I have a comment or clarifying question from Jian at the FDA.

MS. JIAN CONNELL: Yes, Dr. Wade. Thank you. I just want to say, by voting yes, you agree to add the additional warnings about the device improper use and also explaining the magnet behavior. If you vote no, that means you don't recommend

adding additional warning or inform the physicians of the magnet behavior. Thank you.

DR. KELLY WADE: That was very helpful. Thank you. If there's no further discussion on this question, we will now begin the voting process. You should've received an email from the pediatricadvisorycommittee_vote@fda.hhs.gov with voting instructions. Please Reply All to the message and, when responding, only type your vote, yes, no, or abstain, in the body of the message, nothing else. In case you encounter technical difficulties, please email ocoptpacteam@fda.hhs.gov. Please start voting on the Flourish Question one. You will have 60 seconds to respond to the voting question. I neglected to set a timer. Derek if you can let me know when one minute is up.

MS. MARIEANN BRILL: Kelly, this is Marieann Brill. The one minute is up.

DR. KELLY WADE: Thank you. We will now take a 10-minute break while the FDA compiles the votes. The vote will then be displayed on the screen, and the designated federal officer will read the vote from the screen into the record.

[End of Audio 2]

DR. KELLY WADE: Welcome back everyone. It's Kelly Wade. We are ready to see the results if they could be displayed. Marieann, do you need to summarize these results before we do the roll call?

MS. MARIEANN BRILL: Yes, I sure do. Thank you so much for reminding me Kelly.

DR. KELLY WADE: No worries.

MS. MARIEANN BRILL: For the Flourish question number one --

DR. KELLY WADE: I don't seem to be able to hear you, Marieann. I'm not sure if that's a problem for others as well.

DR. SARAH HOEHN: Yeah. I cannot hear her either. It cut out.

DR. VASUM PEIRIS: Yeah. Kelly, I couldn't hear either.

DR. KELLY WADE: Okay. Marieann, can you go back and start again?

MS. MARIEANN BRILL: Sure. This is Marieann Brill. Can you hear me now?

DR. KELLY WADE: I can hear you now.

MS. MARIEANN BRILL: Okay. Wonderful. For the Flourish question number one, we have 13 yes and 1 abstain.

DR. KELLY WADE: Thank you. Now that the vote is complete, we will go down the meeting roster and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We will start with Angela Czaja.

DR. ANGELA CZAJA: Angela Czaja. I voted yes based on the last instructions by the FDA that, if yes, I agree that those should be included, warnings, and a no would indicate that I did not think the warnings should be included. I did want to add the caveat that I thought that those would be necessary but probably insufficient for addressing the concerns about the risk.

DR. KELLY WADE: Thank you. Dr. Dracker?

DR. ROBERT DRACKER: Bob Dracker. I voted yes in support.

DR. KELLY WADE: Dr. Fischer?

DR. GWENYTH FISCHER: Gwen Fischer. I voted yes in support for the same reasons that Dr. Czaja just mentioned.

DR. KELLY WADE: Thank you. Dr. Flick?

DR. RANDALL FLICK: Randall Flick. I voted yes.

DR. KELLY WADE: Dr. Havens?

DR. PETER HAVENS: Peter Havens. I voted yes and support the other comments that have been made.

DR. KELLY WADE: Dr. Hoehn?

DR. SARAH HOEHN: Sarah Hoehn. I voted yes. I agree with the other comments and I agree with Dr. Czaja that we need more warnings. I think we should incorporate what Dr. Flick has highlighted which is the need for qualified pediatric surgery involvement.

DR. KELLY WADE: Dr. Holubkov?

DR. RICHARD HOLUBKOV: Rich Holubkov. I voted yes. I fully support the other comments, the other statements just made. Thanks.

DR. KELLY WADE: Thank you. Dr. Jones?

DR. BRIDGETTE JONES: This is Bridgette Jones. I voted yes. I agree with the other comments and I'd also like to add that I would recommend changing the wording from "would mitigate" to "may" and also that there should be clarification as far as the warnings, specifically that the warnings will be included in the directions for use and also be incorporated in the physician training.

DR. KELLY WADE: Thank you. Dr. Lukish?

DR. JEFFREY LUKISH: I voted yes. I support and agree with all the comments that my colleagues have provided.

DR. KELLY WADE: Dr. McMillan?

DR. GIANNA MCMILLAN: Gianna McMillan. I voted yes and support the other comments.

DR. KELLY WADE: Thank you. Dr. Ortiz-Aguayo?

DR. ROBERTO ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. I voted yes and also support the comments.

DR. KELLY WADE: Randi Oster?

MS. RANDI OSTER: I voted to abstain for the exact reason that everyone stated that they wanted in their yes vote these comments to be added, such as insufficient warnings. My concern was, if I had just voted yes, that it would be lost, and that if I had voted no, it was going to accomplish the opposite. The abstain vote is the one that I believe fully explains to the FDA our expectations to the PAC.

DR. KELLY WADE: Thank you. Jennifer Plumb?

DR. JENNIFER PLUMB: Hi, Dr. Jennifer Plumb. I'm unable to turn on my video. I don't know if you need to see a face for a vote.

DR. KELLY WADE: No. That's fine.

DR. JENNIFER PLUMB: Okay. I also voted yes. I think it'd be pretty hard to sum it up any better than my colleagues have. I think that anything we can do to heighten people's due diligence in thinking about and respectfully and safely using this device is a good one.

DR. KELLY WADE: Thank you. Wael Sayej?

DR. WAEL SAYEJ: Hi, this is Wael Sayej. I voted yes. I echo and agree with the comments mentioned by my colleagues. I have full faith and confidence in the FDA that they will ensure that appropriate warnings are added to the labeling, and I honestly have good faith in Cook, that they will aid the FDA in making sure those warnings are appropriate.

DR. KELLY WADE: Thank you to members of the PAC for that discussion. We can now move onto question two as seen on this voting slide number two. There are multiple clinical factors that can impact the effectiveness of the anastomosis. Does the committee agree that physicians should be given additional information regarding the clinical variables to better identify suitable candidates for the treatment with the Flourish device? The answers are the same: yes, no, and abstain. We will start by any specific questions to the wording of the question. Then we will move on from there.

Hands raised if it's specific comment or question about the wording. If there are no questions or comments concerning the wording of question number two, we will then proceed with the question and open the question for discussion. I would like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Simply raise your hand if you would like to comment or question the voting slide number two before us. Great. Dr. Havens, we'll start with you.

DR. PETER HAVENS: Thank you. Presumably, this would be, with inclusion of this material, in the product label, or did the FDA have something more extensive in mind?

MS. JIAN CONNELL: Thank you for your question. Currently, the additional clinical factors, other than the patient less than one year old and with an atretic gap of less than four centimeters and with those specific esophageal atresia types, other clinical factors are not included. Cook proposed the FDA with this additional clinical factors, as I mentioned earlier, patients anatomy or esophageal pouches and also the placement of a PEG tube where the stoma place is. FDA has a pending question to Cook asking exactly what type of information will be collected at Cook's post-approval study. FDA has not received that response yet. I can defer that question to Cook if you feel that would better clarify your question. Also, we want the panel member to maybe give us some advice on exactly what type of clinical factors you think would be helpful for the physician in selecting patient that would be best to maximize the benefit of the Flourish device.

DR. PETER HAVENS: Then, would this be included in the product label? Would it only occur as a part of the training that Cook currently supplies?

MS. JIAN CONNELL: If based on the collection from the post-approval study that there is enough information to make a recommendation, then yes, that would be included in the labeling.

DR. PETER HAVENS: Okay. You're not considering doing this right now? This would be after further information is collected in the post-approval study?

MS. JIAN CONNELL: Correct. Cook said based on currently limited information and the difficulty to recreate a benchtop model applying to this specific patient factors, it's very difficult to do it currently. They propose to do it when they complete the post-approval study. This is a term for the long run, regarding your

response to the first question, to better improve this device and make it most safe-used device. This is something FDA considering that might be helpful to the physicians. Yes.

DR. PETER HAVENS: Got it. Thank you very much.

MS. JIAN CONNELL: Sure.

DR. KELLY WADE: The next comment or question is from Dr. Flick.

DR. RANDALL FLICK: I think this goes without saying, that we should be supportive of this. Obviously, it depends on what the additional information, what the clinical variables are. I would say that this gets back to my earlier comment that, in the absence of an appropriate comparator, it's difficult to determine what are the clinical variables that will identify suitable candidates. I know that the sponsor's doing the best they can, and I applaud them for that. I think understanding how the device performs relative to similar patients will be very important in determining what variables are relevant. Thanks.

DR. KELLY WADE: Thank you. Dr. Jones?

DR. BRIDGETTE JONES: Bridgette Jones, PAC member. Again, I'm struggling with the language here and from what was earlier described as what this question actually means. It's not that we already know the potential clinical factors that impact but the next step would be for the sponsor to collect more data and then those clinical factors be identified for consideration to be provided to physicians as additional information. To me, this question sounds a little bit premature, a premature step, because it states that there are multiple clinical factors or that that's likely so, but we don't know. We also don't know, depending on what's identified, what should be

provided to physicians. The wording here sounds premature with the current information that we have, unless the sponsor or any of the other panelists can provide more information. Are there clinical factors that we do know about now that you would feel strongly that should be provided to physicians now that we know enough information about?

MS. JIAN CONNELL: From my understanding, no, not yet. Does any Cook representative that would respond to this question, if you have a more clear picture now regarding what kind of variables would impact?

DR. KELLY WADE: Yeah. I welcome clarifying comments from a Cook representative if you'd like to do so.

DR. JEFFREY LUKISH: Yeah. Hi, this is Dr. Lukish. Can you hear me or see me?

DR. KELLY WADE: Yes.

DR. JEFFREY LUKISH: Yeah. The number one clinical factor, if we look at all of the MDRs, is the difference between using the device in children with the type C atresia -- that is the atresia with the distal tracheoesophageal fistula -- and the type A atresia, which is the pure esophageal atresia. Those are the two critical clinical factors where the device will perform differently. It should be clearly described to the physicians that are entertaining using this device. By clarifying that to the physicians that are using this device, that will be articulated to the IRB during the approval phase of the HDE.

We've already outlined other clinical factors, gap width of the atresia. We know that atresias that are greater than four centimeters can't be brought together with

this, can't be utilized. Then we talked about also how we are determining that gap width. Those pieces need to be described in the labeling because they are predictive of the effectiveness of the device in creating an anastomosis. I hope that clarifies.

DR. TED HEISE: Dr. Wade, this is Ted Heise, the sponsor.

DR. KELLY WADE: Thank you. Yes, you're welcome to provide comment.

DR. TED HEISE: Yes. Thank you for the question. As we discussed previously with Dr. Lukish and as he just reiterated, there is I think a strong likelihood that prior surgeries associated with correction of type C atresia before use of the Flourish device is very likely to reduce likely chance of success. Understandably and appropriately, FDA typically expects data to support labeling changes. We don't have specific data to support such a change. We do hope to get it from the PAS data collection that's underway. Even with 20 cases, it's not clear that that data will be completely adequate to support such a labeling change. I think we'll just have to see what we get when we get it.

DR. KELLY WADE: Do you have a comment?

MS. JIAN CONNELL: Yes, Dr. Wade. I want to ask Ted if currently you have any specific factors in mind that you collect during your post-approval study.

DR. TED HEISE: Yes. This is Ted Heise with the sponsor. I do think prior surgery is a definite candidate, one we want to look at carefully. Other options could be the type of angulation that may be in place between the gastrostomy and the gastric pouch and whether that compromises the ability to achieve a suitable alignment. That'll be a much more challenging variable to assess. We'll have to rely on what we

can get out of imaging, which is somewhat challenging when you're dealing with maybe at most two views of plain radiographs.

MS. JIAN CONNELL: Thank you, Ted. I know there is a PAC member commenting. This might be pretty much your question, but FDA take this as an opportunity. Based on the small number of the patient who currently use the device and limited information collected, we may not be able to make a conclusion yet. I thought this is an opportunity for us to collect additional data in the post-approval study. Therefore, we already make up our minds that certain information is important and needed for the future patient's use of the device.

Then I would think, why not take this opportunity and collect all this information, and then we complete a study that won't be too late we said, "Oh, PAS already completed. We can't do additional thing." To avoid that, I would rather propose to do it now so when it's conclude, the study, we'll have better information about what's the best recommendation we should provide so the physician would have a more informed use of the device.

DR. KELLY WADE: Thank you. That was helpful. Dr. Dracker?

DR. ROBERT DRACKER: Actually, what Jian just mentioned was exactly what I was going to suggest. Given the small number of patients who have had the procedure and the fact that clinical variables are going to be increasing with time, it needs to be a concurrent and dynamic approach providing physicians with information as they change, supporting really what Bridgette had said as well, that it's really too early to tell or to give advice to clinicians. As long as the company's collecting data and providing the utmost and most concurrent information to the physicians involved with

utilizing the device, I think it makes no sense.

DR. KELLY WADE: Thank you, Bob. I agree as well. It's Kelly Wade. I would just add, too, that we really need to make all efforts of enrolling those patients that had these adverse events because, if we don't have them in our post-marketing study, then we won't have the critical information together to know really where the warnings need to lie. Really I think, again, multiple members of the committee have talked about the importance of enrolling as many patients as we can in the post-marketing study. If there are no further discussion on this question, then we will now begin the voting process.

You should've received an email from the pediatricadvisorycommittee_vote@fda.hhs.gov with voting instructions as you did with the prior question. Please Reply All to the message. When responding, only type your vote, yes, no, or abstain in the body of the message, nothing else. In case you enter technical difficulties, please email the ocoptpacteam@fda.hhs.gov. We will start voting on Flourish question number two. You have 60 seconds.

MS. MARIEANN BRILL: Kelly, this is Marieann Brill. The one minute is up.

DR. KELLY WADE: Thank you. This completes our voting. We will now take a 10-minute break while the FDA compiles the votes. The vote will then be displayed on the screen, and the designated federal officer will read the vote from the screen into the record. This will begin our 10-minute break.

[BREAK]

DR. KELLY WADE: Kelly Wade. Welcome back everyone. This

concludes our break. We will now show the results of vote number two. Marieann Brill, the designated federal officer, will summarize the results.

MS. MARIEANN BRILL: For the vote in question number 2 for the record, there are 14 yes, zero no, zero abstain. Again, 14 yes, zero no, zero abstain. Thank you.

DR. KELLY WADE: Thank you. Now that the vote is complete, we will go down the meeting roster and have everyone who voted state their name, their vote, and if you want to, you can state the reason why you voted as you did into the record. We will start with Angela Czaja.

DR. ANGELA CZAJA: Angela Czaja, member of the PAC. My vote was yes.

DR. KELLY WADE: Bob Dracker.

DR. ROBERT DRACKER: Bob Dracker. I agreed and voted yes with the caveat that data continues to be updated and provided to the clinicians.

DR. KELLY WADE: Dr. Fischer.

DR. GWENYTH FISCHER: Gwen Fischer. I voted yes.

DR. KELLY WADE: Dr. Flick.

DR. RANDALL FLICK: Randall Flick. I voted yes.

DR. KELLY WADE: Dr. Havens.

DR. PETER HAVENS: Peter Havens. I voted yes.

DR. KELLY WADE: Dr. Hoehn.

DR. SARAH HOEHN: Sarah Hoehn. I voted yes.

DR. KELLY WADE: Dr. Holubkov.

DR. RICHARD HOLUBKOV: Rich Holubkov I voted yes.

DR. KELLY WADE: Bridgette Jones.

DR. BRIDGETTE JONES: Bridgette Jones. I voted yes.

DR. KELLY WADE: Jeffrey Lukish.

DR. JEFFREY LUKISH: I voted yes. Can you hear me?

DR. KELLY WADE: Yes.

DR. JEFFREY LUKISH: Yeah. Perfect.

DR. KELLY WADE: Thank you. Gianna McMillan.

DR. GIANNA MCMILLAN: Gianna McMillan. I voted yes.

DR. KELLY WADE: Thank you. Roberto Ortiz-Aguayo.

DR. ROBERTO ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. I voted yes.

DR. KELLY WADE: Thank you. Randi Oster.

MS. RANDI OSTER: Randi Oster and I voted yes.

DR. KELLY WADE: Jennifer Plumb.

DR. JENNIFER PLUMB: Jennifer Plumb and I voted yes.

DR. KELLY WADE: Thank you. Wael Sayej.

DR. WAEL SAYEJ: Wael Sayej and I voted yes.

DR. KELLY WADE: Thank you everyone. We will now move on to question number three. Question number three is on the slide now. It states, "The FDA will report on the following to the PAC in 2022: the annual distribution number, the PAS follow-up results, an MDR review, and a literature review." Does the committee agree with the FDA's plan for continued surveillance of the Flourish device? As usual, we will start with questions specifically addressing the wording of this question before

us. After that, we will move into further comment and question regarding the topic itself. Are there any clarifying questions about the wording of the question?

Okay. If there are no questions or comments concerning the wording of question number three, we will now proceed with the question and open the question for further discussion. I would like to remind public observers that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. The first raised hand I'll call on, Randi Oster.

MS. RANDI OSTER: Yes. Thank you. Randi Oster, consumer representative. I'm wondering if in the bullets we could add in some of the data that we've been talking about today, specifically the breakdown and the segregation of the patient population from the pure to the other kinds of issues that they have, the comorbidities, as well as requesting an understanding of the doctor's and the number of times they've done this to see if there's any correlation between repeat surgeries and learning and the reduction of the adverse events.

DR. LAUREN MIN: This is Lauren Min from FDA. I'll start by addressing your comment about the type of esophageal atresia. That information is being systematically collected from medical records in the post-approval study, which is why we've been saying throughout the day that it's of the utmost importance to get these patients, as many of them as possible, enrolled in the PAS. Outside of this mandated study, I believe that in the non-PAS patients that data will continue to be collected anecdotally as that information is relayed from the treating physicians and the healthcare providers to Cook. On your point about experience of the doctors, that's not something that's required reporting from the FDA's perspective. Perhaps Ted from Cook or another

company representative could address your second point.

DR. KELLY WADE: It's Kelly Wade. If a Cook representative would like to address that comment, you're welcome to speak into the record.

DR. TED HEISE: Thank you, Dr. Wade. Ted Heise for the sponsor. We do have a number of variables on the plan for the PAS data collection, including the type of unrepaired atresia, if the patient had a TEF verification of successful repair and time from repair, the procedures performed to reduce the gap prior to device placement, as well as information on prior thoracic surgical procedures, for example, that may HAVE involved the esophagus. We do not have any specific information regarding the specialty or training of the physicians carrying out the procedures. I expect we can probably get that information, though. Thank you.

DR. KELLY WADE: Thank you. Dr. Havens.

DR. PETER HAVENS: Thank you very much. The first question is will this be the last opportunity for the FDA to review the PAS results, and what if there's an inadequate number of patients included in the PAS?

DR. LAUREN MIN: This is Lauren Min from the FDA. The PAS study will close after the company has met its requirement of providing complete data in 20 patients. As we mentioned before and as Cook has mentioned, we expect that data collection to be completed by the end of next year, which means we hope to provide much of those results to share them with the PAC during fall of 2022. I don't believe it'll be a complete dataset at that point. I believe that in the following year we'll have a complete post-approval study, hopefully. PAS enrollment and data collection will continue until Cook has completed the requirements for that study, which again is 2

years of follow-up or follow-up until study exit in 20 patients. We're really counting on that data to learn more about the safety and effectiveness of the device, particularly concerned about some of the safety issues that we've been talking about today. We'll present more during the next PAC and hopefully a full PAS dataset in 2023.

DR. PETER HAVENS: Thank you. I would urge FDA to consider that its power under the HDE to include an IRB at each site and your ability to demand data collection be used to enhance reporting activity at the sites. This would not necessarily delay anybody's use of the product. In fact, when I want to use an experimental antimalarial that I have to get from the CDC, it is demanded that I get an IRB and it's demanded that I make a report. That could be a part of the use of these. There is no more willing partner than Cook at working with the FDA. They've shown that over and over. This would be a way for the FDA to use its power under the HDE to enhance reporting. This is a critical issue not just for this device but in many things used for rare pediatric diseases. Thank you.

DR. KELLY WADE: Thank you, Peter. Kelly Wade. I'm wondering if I can direct the same topic and a question back to Lauren at the FDA. I was wondering if it's possible to do a preliminary look at that retrospective PAS because they're about 50 percent enrolled right now. I want to make sure that we're able to capture infants that had some of these adverse events because, if we don't have enough of the adverse events in that dataset, it won't be able to inform us with the information that we're looking for. Even a quick preliminary look to see if there are significant adverse events in the dataset may be important now so that moving forward, if more efforts are needed to include certain outcomes, we can do that work now rather than at the end. Can you speak to

that, Lauren?

DR. LAUREN MIN: Sure. Currently, Cook is required to provide biannual reports. I believe their next PAS interim report is due next month, which is great. That will be our next chance to look at, as you said, close to half of the patients that are required for the post-approval study. We're looking forward to that data. The next look will be six months later. So that the committee is aware, we're not waiting full year to have eyes on these data, and we'll continue to communicate with Cook about concerns with MDRs or other issues that are reported as we see them come in.

DR. KELLY WADE: Thank you so much.

DR. LAUREN MIN: Sure.

DR. KELLY WADE: Are there any other clarifying comments or questions from members of the PAC? Okay then, if there is no further discussion on this question number three, we will now begin the voting process. You should've received an email from the Pediatric Advisory Committee Vote with voting instructions. Please Reply All to the message. When responding, only type your vote, yes, no, or abstain, in the body of the message, nothing else. In case you encounter technical difficulties, remember to email the ocoptpacteam@fda.hhs.gov. We will start the voting on the Flourish question number 3, and again you'll have 60 seconds to respond to the vote.

Thank you. This concludes the voting window. We will now take a 10-minute break while the FDA compiles the votes. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the record. This will begin our last 10-minute break.

[BREAK]

DR. KELLY WADE: This is Kelly Wade. The vote is complete and the results are read to display. Unless there are objections, I'm going to bring us back form break two minutes early so that we may also adjourn this meeting on time. Let's see the results. The results are shown on your screen, and Marieann will read them into the record.

MS. MARIEANN BRILL: Thank you. For the final question, question number 3, for the record there are 14 yes, zero no, zero abstain. Again, 14 yes, zero no, zero abstain. Thank you.

DR. KELLY WADE: Thank you. Now that the vote is complete, we will go down the meeting roster and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. Angela Czaja.

DR. ANGELA CZAJA: Angela Czaja. My vote was yes.

DR. KELLY WADE: Bob Dracker.

DR. ROBERT DRACKER: Bob Dracker. My vote is yes.

DR. KELLY WADE: Gwen Fischer.

DR. GWENYTH FISCHER: Gwen Fischer. My vote was yes.

DR. KELLY WADE: Thank you. Randall Flick.

DR. RANDALL FLICK: Randall Flick. My vote was yes.

DR. KELLY WADE: Peter Havens.

DR. PETER HAVENS: Peter Havens. I voted yes.

DR. KELLY WADE: Sarah Hoehn.

DR. SARAH HOEHN: Sarah Hoehn. I voted yes.

DR. KELLY WADE: Richard Holubkov.

DR. RICHARD HOLUBKOV: Rich Holubkov. I voted yes.

DR. KELLY WADE: Bridgette Jones.

DR. BRIDGETTE JONES: Bridgette Jones. I voted yes.

DR. KELLY WADE: Thank you. Jeffrey Lukish.

DR. JEFFREY LUKISH: Jeffrey Lukish. I voted yes.

DR. KELLY WADE: Gianna McMillan.

DR. GIANNA MCMILLAN: Gianna McMillan. I voted yes.

DR. KELLY WADE: Roberto Ortiz-Aguayo.

DR. ROBERTO ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. I voted yes.

DR. KELLY WADE: Randi Oster.

MS. RANDI OSTER: This is Randi Oster. I voted yes but I want to go on record that I appreciated the sponsor's willingness to look at the doctors' experience. We discussed today training is an important component of reducing adverse events. I would like that training or the doctor experience to be considered as one of the bullet points in addition to the ones that are there.

DR. KELLY WADE: Thank you. Jennifer Plumb.

DR. JENNIFER PLUMB: Jennifer Plumb. I voted yes.

DR. KELLY WADE: Thank you. Wael Sayej.

DR. WAEL SAYEJ: Wael Sayej. I voted yes and I completely agree with Randi's comments. I am happy with the sponsor's participation so far. Thank you.

ADJOURNMENT

DR. KELLY WADE: Well, thank you everyone. Before we conclude this meeting, this is Kelly Wade and I would like to thank the members of the PAC for their engaging discussion today and participation. I would also like to thank the members of the FDA and the sponsor for the excellent background materials that were provided to us today and the excellent presentations provided as well. I think this has been an important day for us to come together to review the update regarding the Flourish device and to think about outcomes as they regard to successful anastomosis but also safety concerns of adverse events, including those in the MDR.

As you've heard from our discussion today, the committee supports the inclusion of additional warnings in device label, instruction for use, and physician training. Additional warning is an important first step in the ongoing work to optimize patient selection and minimize improper device use and manipulation. I applaud your efforts that are ongoing to gather the necessary data to inform optimal use and patient selection and limit the adverse events in this critical population. We are keenly interested in the clinical variables and site expertise factors associated with successful anastomosis and the safety of device use, including the minimization of adverse events including perforation and the minimization of strictures. I will bring this meeting to a conclusion with that and thank everyone for their participation today.

MS. JIAN CONNELL: I also want to thank the chairperson, Dr. Wade, and all the PAC members on behalf of our FDA team. We appreciate your time and expertise and we value your opinions. We take it seriously. We also thank Cook for the

cooperation with FDA. FDA will continue work with Cook to best improve this device for safe use and optimize use for other uses. Thank you.

DR. KELLY WADE: Thank you very much.

[WHEREUPON THE MEETING WAS ADJOURNED]