Study Title: Fetal Endoscopic Tracheal Occlusion (FETO) Trial for Congenital Diaphragmatic Hernia (CDH)

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National Clinical Trial (NCT) Identified Number: 04052828

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with Good Clinical Practice and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Fetal Endoscopic Tracheal Occlusion (FETO) Trial for Congenital Diaphragmatic Hernia (CDH)

Study Description: This is a single site, single arm, non-randomized, pilot trial to assess the feasibility and safety of treating severe CDH with Fetal Endoscopic Tracheal Occlusion (FETO) at Michigan Medicine.

Objectives:

Primary Objectives:

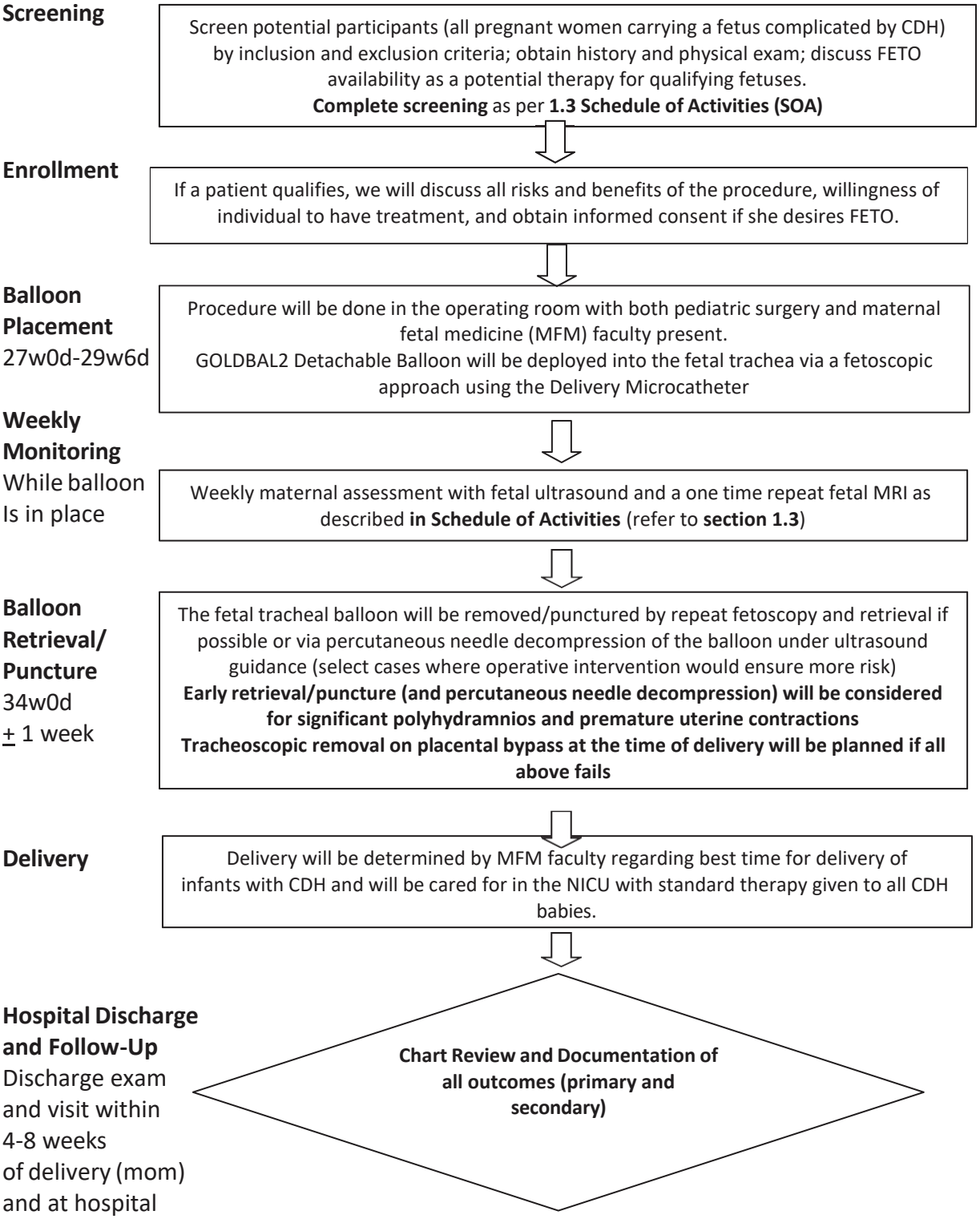
1. Successful placement of the balloon
2. Successful retrieval/puncture of the balloon

Secondary Objectives:

1. Fetal lung volume growth on prenatal imaging measured by observed-to-expected total fetal lung volume (o/e TFLV)
2. Fetal lung growth on prenatal ultrasound measured by observed-to-expected lung to head ratio (o/e LHR)
3. Gestational age at delivery
4. Determining the percentage of neonates that survive to hospital discharge or up to 180 days of life
5. Maternal complications (preterm labor, preterm rupture of membranes (PROM), premature preterm rupture of membranes (PPROM), oligohydramnios, polyhydramnios, placental abruption, chorioamniotic separation, chorioamnionitis, and other infection)

Endpoints:	Primary Endpoints: 1. Successful placement of the balloon at gestational age 27w0d – 29w6d; success will be defined as completion with direct visual placement above the carina and confirmation on ultrasound done during the procedure 2. Retrieval will ideally be at gestational age of 34w0d ± 1 week but success will be defined by retrieval or puncture prior to delivery, including tracheoscopic removal or puncture on placental bypass at time of delivery, either by standard Cesarean section or an ex-utero intrapartum therapy (EXIT) procedure Secondary Endpoints: 1. Fetal MRI prior to balloon placement and 2nd fetal MRI at ± 2 weeks of balloon retrieval 2. Fetal ultrasound o/e LHR before balloon placement and immediately prior to balloon removal 3. Delivery 4. Neonatal discharge from hospital or up to 180 days post-delivery if still hospitalized 5. Maternal postpartum discharge and follow-up to determine maternal complications
Study Population:	Pregnant women carrying a fetus complicated by CDH who are evaluated at the Fetal Diagnosis and Treatment Center (FDTC) at Michigan Medicine.
Phase:	Feasibility and safety
Description of Sites/Facilities Enrolling Participants:	The Fetal Diagnosis and Treatment Center (FDTC) is a comprehensive multidisciplinary fetal treatment center. Evaluation and treatment is provided at co-localized Von Voigtlander Women's Hospital and C.S. Mott Children's Hospital. Team members include experts in pediatric surgery, maternal fetal medicine, neonatology, pediatric anesthesia, pediatric cardiology, genetic counselors, pediatric radiology, social work, and others as needed for individual fetal diagnoses.
Description of Study Intervention:	A Goldballoon Detachable Balloon (GOLDBAL2) will be inserted into the fetal trachea and deployed with the Delivery Microcatheter (BALTACCI-BDPE100). These are both manufactured by Balt Extrusion (Montmorency, France).
Study Duration:	48-60 months is estimated to enroll up to 10 patients. Data will be analyzed after delivery of the 10th patient for primary outcomes. Analysis of all secondary outcomes will require that the infants are discharged from the hospital or 180 days post-delivery if still hospitalized.
Participant Duration:	The FETO balloon will ideally be in place 4-8 weeks depending on maternal safety for those that meet inclusion criteria. Mothers will need to participate in weekly evaluations during this time and up to delivery. Mothers will be followed until their postpartum discharge appointment. Infants will be followed through hospital discharge, death, or 180 days of life (whichever occurs first).

1.2 SCHEMA


Screening
Screen potential participants (all pregnant women carrying a fetus complicated by CDH) by inclusion and exclusion criteria; obtain history and physical exam; discuss FETO availability as a potential therapy for qualifying fetuses.
Complete screening as per 1.3 Schedule of Activities (SOA)
Enrollment
If a patient qualifies, we will discuss all risks and benefits of the procedure, willingness of individual to have treatment, and obtain informed consent if she desires FETO.
Balloon Placement
27w0d-29w6d
Procedure will be done in the operating room with both pediatric surgery and maternal fetal medicine (MFM) faculty present.
GOLDBAL2 Detachable Balloon will be deployed into the fetal trachea via a fetoscopic approach using the Delivery Microcatheter
Weekly Monitoring
While balloon Is in place
Weekly maternal assessment with fetal ultrasound and a one time repeat fetal MRI as described in Schedule of Activities (refer to section 1.3)
Balloon Retrieval/ Puncture
34w0d
± 1 week
The fetal tracheal balloon will be removed/punctured by repeat fetoscopy and retrieval if possible or via percutaneous needle decompression of the balloon under ultrasound guidance (select cases where operative intervention would ensure more risk)
Early retrieval/puncture (and percutaneous needle decompression) will be considered for significant polyhydramnios and premature uterine contractions
Tracheoscopic removal on placental bypass at the time of delivery will be planned if all above fails
Delivery
Delivery will be determined by MFM faculty regarding best time for delivery of infants with CDH and will be cared for in the NICU with standard therapy given to all CDH babies.
Hospital Discharge and Follow-Up
Discharge exam and visit within 4-8 weeks of delivery (mom) and at hospital discharge or 180 days of life (baby)
Chart Review and Documentation of all outcomes (primary and secondary)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Prenatal Plan							
	Screening	**Enrollment** (within 1 week of balloon placement)	**Balloon Placement** (27w0d to 29w6d)	**Monitoring** (placement to retrieval)	**Balloon Retrieval/ Puncture** (34w0d + 1 week)	**Monitoring** (retrieval/puncture to delivery)	**Delivery**
Maternal Demographics*	x						
Confirmation of diagnosis with comprehensive US including o/e LHR*	x						
Inclusion/Exclusion Criteria Reviewed	x	x					
Maternal History*	x						
Interval Maternal History*		x		Weekly		x	x
Maternal Exam*	x						
Interval Maternal Exam*		x		Weekly		x	x
Counseling with MFM, CGC*	x						
Invasive testing* (Microarray, Karyotype)	x						
Fetal MRI*	x				X** (If needed to confirm balloon deflation)		
Fetal Echocardiogram*	x						
Evaluation with multi-disciplinary team*	x						
Maternal screening for substance abuse and depression (via EPDS)*	x						
Maternal labs: CBC, type and screen, antibody screen, HIV, HBV, HCV*	x						
Informed Consent (Study Participation)		x					
Surgical Consent		x			x		

FETO (balloon placement)			x				
US for fetal assessment including amniotic fluid, membrane status, fetal well-being, o/e LHR*		x		Weekly for remainder of pregnancy (including balloon visualization)		Weekly for remainder of pregnancy	
US includes growth and anatomy overview*				Every 3 weeks		Every 3 weeks	
2nd Fetal MRI (measure lung growth)**				±2 weeks of balloon retrieval/puncture			
Additional fetal antenatal surveillance*				Weekly		Weekly	
Balloon retrieval/ puncture					x		
Delivery*							x
* Standard of Care							

CBC = complete blood count; CGC = certified genetic counselor; EPDS = Edinburg Postnatal Depression Scale; FETO = fetal endoscopic tracheal occlusion; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; o/e LHR = observed-to-expected lung to head ratio; MFM = maternal fetal medicine; MRI = magnetic resonance imaging

**Ideally 2nd Fetal MRI will be done prior to balloon retrieval/puncture. In select cases, it may not be able to be completed prior to retrieval and may be done up to 2 weeks after retrieval. Additional MRIs may be performed as needed for clinical or research reasons (e.g. following intrauterine balloon puncture to confirm deflation, assuming the patient is clinically stable).

Postnatal Plan				
	Infant Birth	**Postpartum Maternal Discharge**	**Postpartum Maternal Follow-up**	**Infant Discharge or 180 Days of Life**
Maternal Exam*		x	x	
Evaluation for maternal complications*		x	x	
Neonatal History*	x			x
Infant Demographics*	x			
Infant Exam*	x			x
* Standard of Care				

2 INTRODUCTION

2.1 STUDY RATIONALE

Congenital diaphragmatic hernia (CDH) affects 1 in 2,200 to 5,000 live births per year (1, 2). The defect in the fetal diaphragm allows abdominal organs (intestine, stomach, liver, spleen) to migrate into the thorax, hindering normal lung development. The herniated contents place pressure on the developing lungs and this may result in varying degrees of pulmonary hypoplasia and associated pulmonary hypertension; both of which may be lethal. In an attempt to prenatally quantify the impact of the herniated organs on underlying lung development, prognostic tools have been developed. The most widely used prognostic indicator is lung-to-head ratio (LHR) as measured by prenatal ultrasound (3-5). The lung contralateral to the diaphragmatic defect is measured in a transverse plane at the level of the four chamber heart and its area is divided by the fetal head circumference (LHR). The LHR is tracked through the pregnancy but seems to be most strongly correlated with outcomes in the early third trimester. An observed-to- expected LHR (o/e LHR) can be calculated and may be more predictive than an isolated LHR as this percentage should not change throughout gestation (6). Fetuses with severe pulmonary hypoplasia (defined as o/e LHR <25%) and those with moderate hypoplasia (o/e LHR 25-<30%) complicated by liver up in the thorax have survival rates under 30% (7).

2.2 BACKGROUND

Fetal intervention for CDH began in the 1990s with open fetal surgical repair of the diaphragmatic defect (8, 9). Open repair of liver-down CDH was successful but found no difference in survival, compared to postnatal repair, primarily due to increased rates of prematurity in the fetal repair group and the fact that liver-down CDH was less severe and postnatal management improved for this group of patients (10). Refinement in prenatal prognostication revealed that in addition to low LHR, it was the subset of liver-up patients that were most severe and the best candidates for fetal surgery. Open repair of liver-up CDH was plagued with high risk of fetal death during repair due to kinking of the umbilical vein when the liver was acutely reduced (9). As such, a new prenatal strategy was required for liver-up CDH patients. It was noted that patients with congenital high airway obstruction syndrome (CHAOS) had hyperplastic lungs due to tracheal occlusion. This strategy was adapted to treat fetal CDH, and research has shown that fetal tracheal occlusion results in fetal lung growth with return of the herniated organs into the fetal abdomen (11). A fetal lamb model of CDH with subsequent tracheal occlusion has demonstrated this to be an effective way to improve lung volume as well as functional improvement in the lung (12-14). These favorable results in an animal model prompted a clinical translation of fetal tracheal occlusion to be used as a prenatal intervention for CDH patients while reducing maternal risks associated with open repair.

In the past 20 years since the abandonment of hysterotomy for tracheal clip placement, multiple techniques have been attempted (15-18). Multi-port fetoscopic clip placement was abandoned due to technique associated morbidity, premature delivery, and the difficulty of removing the tracheal clips to establish an airway at the time of delivery (19). The development of the detachable balloon allows a fetoscopic approach, which markedly reduces maternal morbidity, and allows removal of the balloon late in gestation prior to the delivery, facilitating establishment of the neonatal airway with limited damage to the fetal trachea (20, 21). The GOLDBAL2 detachable balloon from Balt Extrusion (Montmorency, France) is currently being used in the international fetal community with successful balloon placement and

retrieval for fetal CDH. However, the impact on survival in CDH is still being evaluated. International studies in different fetal centers have mixed results with some centers showing benefit of FETO for improved survival and others showing no benefit (17, 18, 22). Currently, there is insufficient evidence to recommend FETO as the standard of care (23). Investigations are still ongoing with multiple institutions in the United States, Europe, and South America participating in the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial (ClinicalTrials.gov, NCT01240057). The TOTAL trial is a randomized trial of FETO vs expectant postnatal management of both moderate and severe CDH (24). In order to participate in the trial, an institution must complete at least 10 FETO cases at their institution and be willing to randomize patients to either arm of the study.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Although FETO has shown increase in fetal lung growth with potential for increased neonatal survival, it does not occur without risks (25). A 2016 systematic review and meta-analysis showed that the most common complications associated with FETO was increased risk of preterm birth (72.4% born before 37 weeks and 17.9% born before 32 weeks) and premature rupture of membranes (46.8% PROM). Less frequent complications were reported as chorioamnionitis (2.6%) and placental abruption (1.2%)(23).

FETO Procedure (balloon placement and retrieval/puncture) and/or tracheoscopic removal on placental bypass during standard Cesarean section, EXIT Procedure, or during precipitous vaginal delivery

Maternal risks:

- Premature rupture of membranes (PROM)
- Polyhydramnios
- Amniotic fluid leakage into the abdomen amniotic fluid leakage into the abdomen with resultant oligohydramnios
- Chorioamnionitis
- Chorioamniotic membrane separation
- Other infection
- Bleeding with possible need of blood transfusion
- Allergic reaction to latex
- Complications associated with anesthesia/analgesia
- Psychosocial stress
- Placental abruption
- Amniotic fluid embolism with resultant respiratory failure
- Deep venous thrombosis that may lead to pulmonary embolism and respiratory failure
- Maternal death

Fetal/neonatal risks:

- Preterm birth with associated complications of prematurity
- Fetal or neonatal death associated with the removal procedure (inability to remove or puncture balloon)
- Adverse tracheal effects from the balloon including epithelial damage, cartilage and/or muscle damage, tracheomegaly, tracheomalacia, etc.

- Morbidity after birth which may be increased by the procedure as it allowed survival or treated pulmonary hypoplasia at the expense of complications of prematurity
- Failure to enter the uterus/trachea or position the balloon adequately
- Vocal cord injury
- Injury to fetal neck or trachea from percutaneous balloon puncture or balloon removal
- Balloon migration out of trachea with potential to be swallowed, requiring additional evaluations to monitor location and/or procedures to remove if it causes obstruction or any other complications from retention
- Balloon remnants, or intact/inflated balloon, remaining in the airway, potentially requiring additional evaluations to monitor location before or after birth and/or procedures after birth to remove if it causes obstruction or any other complications from retention
- MRI evidence of failed ultrasound guided balloon puncture or inability to carry out an MRI following ultrasound guided balloon puncture requiring specialized cesarean delivery.
- Complications associated with anesthesia/analgesia
- Spontaneous intrauterine fetal demise/death

ECMO

Complications of ECMO support for neonate including:

- Complications associated with insertion of the cannulas into the vessels (bleeding, infection, and injury or ligation of the blood vessels during cannulation and decannulation that may result in stroke, brain damage, or death)
- Bleeding risk due to need for systemic anticoagulation (resulting in bleeding into the brain or other tissues that cause permanent damage)
- Increased requirement for blood transfusion
- Requirement of additional surgeries, or death)
- Machine failure (e.g. the circuit may clot requiring circuit change and the patient may not be able to survive the procedure of changing the circuit)
- Multiple organ system failure
- Blood clots (resulting in stroke or multiple organ system failure)
- Infection

Drug Risks

Indomethacin (given at balloon placement)

Maternal Risk

- Dizziness
- GI distress including heartburn, nausea, vomiting, and inflamed stomach lining

Fetal/Neonatal risk

- Early narrowing or closure of ductus arteriosus
- Decreased responsiveness to postnatal indomethacin for closure of persistent patent ductus arteriosus
- Possible increased risk of necrotizing enterocolitis
- Possible impact on renal function due to oligohydramnios
- Possible increased risk of intraventricular hemorrhage or periventricular leukomalacia
- Oligohydramnios

Betamethasone (given prior to balloon retrieval as this medication is a steroid that will help develop the fetus' lungs due to risk of preterm delivery)

Maternal Risk

- Allergic reaction causing wheezing, chest tightness, swelling of face/lips/tongue/throat, or seizure
- Infection at the injection site
- Elevated blood glucose

Fetal/Neonatal Risk

- No known risks with single course

Nifedipine (may be given after first procedure to decrease risk of preterm delivery)

Maternal Risk

- Allergic reaction causing wheezing, chest tightness, swelling of face/lips/tongue/throat
- Headaches
- Hypotension
- Rarely may be associated with temporary elevations in enzymes such as AST, ALT

Fetal/Neonatal Risk

- No known risks at clinical dose used in humans

Since the inception of fetal surgery, there has been concern regarding maternal wellbeing during the index pregnancy and with future pregnancies (26). A recent survey of women who had undergone FETO versus expectant management for a CDH pregnancy was completed. Although the response rate was only 40%, there was no evidence of worse outcomes for the fetoscopy group. Specifically, no one reported subsequent fertility problems and subsequent pregnancies had the same rate of congenital anomalies or complications as the normal population (27).

Of note, fetoscopic procedures are done during pregnancy for a wide range of indications and there is no evidence to date that these procedures, in general, have an adverse impact on subsequent obstetric outcomes. In summary, we expect that FETO will be associated with increased preterm birth and PROM. We will monitor for rare complications of chorioamnionitis and placental abruption. We do not expect long term complications with future pregnancies.

2.3.2 KNOWN POTENTIAL BENEFITS

FETO has shown to increase prenatal lung volumes and prenatal lung perfusion (28, 29). Hypothetically, these will counteract the two major problems associated with CDH, namely pulmonary hypoplasia and pulmonary hypertension. Although individual studies show mixed results, a 2016 systematic review showed increased neonatal survival in severe CDH patients who underwent FETO. Specifically, the relative risk comparing FETO to expectant management was 5.8 (1.5-22.9) for 30 day survival and 10.5 (1.5-74.7) for 6 month survival (23).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although there are known risks of the procedure (preterm labor, PROM, PPROM, oligohydramnios, polyhydramnios, placental abruption, chorioamniotic separation, chorioamnionitis, and other maternal

infection), the potential for increased lung volume and neonatal survival in a condition with such high mortality makes complete and transparent counseling extremely important. Patients will be counseled regarding all potential risks and benefits including uncertain benefit of their fetus and the potential prematurity to which makes lethality more likely. We will only include patients with severe diaphragmatic hernia and we will adhere strictly to inclusion criteria, including excluding patients at increased risk of premature delivery or with signs of placental abruption. Fetal screening will also be thorough to exclude fetuses with known conditions that would limit survival and, therefore, would have limited benefit from the prenatal therapy. Antibiotics and sterile technique will be used during the procedure to decrease infectious risk. Long-term risks to the mother or her future reproductive potential are not anticipated but will be discussed as a hypothetical risk. There is risk of premature balloon removal for maternal reasons or fetal distress (see **Section 6.5.1**) which may limit the degree of fetal lung growth.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. Successful placement of the GOLDBAL2 balloon	1. Placement: Gestational age of 27w0d – 29w6d	1. This timing optimizes lung growth in the late canalicular and early saccular phases of fetal lung growth.
2. Successful retrieval or puncture of GOLDBAL2 balloon	2. Retrieval/ Puncture: Gestational age of 34w0d ± 1 week	2. Removal or puncture of the balloon prior to delivery is important in order to avoid an airway emergency at birth. Ideally this occurs around the 34th week of gestation to optimize lung growth but have the balloon removed prior to delivery. Furthermore, studies demonstrate enhanced lung development when the balloon is removed prior to birth. We include successful tracheoscopic removal or puncture on placental bypass, either during standard Cesarean section or EXIT procedure, as a success if within 34w0d ± 1 week.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
1. Fetal lung volume growth on prenatal MRI	1. Fetal MRI done prior to balloon placement and again done ±2 weeks of balloon retrieval/puncture	1. Fetal MRI will measure the o/e TFLV at each MRI. Fetal lung growth (difference between 1st and 2nd MRIs will be calculated).
2. Fetal lung growth on prenatal ultrasound	2. Fetal ultrasound done before balloon placement and immediately prior to balloon retrieval/puncture	2. Prenatal ultrasound will measure the o/e LHR at weekly visits while the balloon is in place. Fetal lung growth will be calculated as the difference between the o/e LHR pre-balloon placement and the o/e LHR immediately prior to balloon removal/puncture
3. Gestational age at delivery	3. Delivery	3. Preterm delivery is a known risk of FETO. Gestational age at delivery will be an important marker in this trial of safety and feasibility.
4. Survival to hospital discharge or 180 days	4. Discharge from hospital or 180 days of life	4. Survival to hospital discharge will be important as this is a proposed benefit of FETO. We will analyze survival at 180 days for those still hospitalized at that time point.
5. Maternal complications (preterm labor, PROM, PPROM, oligohydramnios, polyhydramnios, placental abruption, chorioamniotic separation, chorioamnionitis, and other infection)	5. Maternal postpartum discharge and follow-up (4-8 weeks after delivery)	5. Known maternal complications can occur during the pregnancy and/or at delivery. Upon discharge post-delivery and at post-partum visit, all potential complications will be assessed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single site, single arm, non-randomized pilot trial to assess the feasibility and safety of treating severe CDH with Fetal Endoscopic Tracheal Occlusion (FETO) at Michigan Medicine.

CDH is a potentially lethal disease that results in pulmonary hypoplasia and pulmonary hypertension with an incidence of almost 1 in 2,500 US births (30). FETO has been shown to increase fetal lung volume with a potential increase in neonatal survival (23, 25). The procedure is done in only a few US fetal centers and continues to be investigational.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A feasibility and safety trial is chosen as the GOLDBAL2 detachable balloon is not FDA approved and its use in the FETO procedure is investigational. Although tracheal balloon placement has not been previously performed at Michigan Medicine, our FDTC team has extensive experience in fetoscopy for multiple other fetal interventions. This would be an additional procedure that could be offered to our patients with a life-threatening disease.

4.3 JUSTIFICATION FOR INVESTIGATION

Fetuses with severe CDH have a high risk of mortality. The current standard of care treatment offers postnatal repair and this is associated with an overall survival of 71% in all cases. A majority (68%) of fetuses are prenatally diagnosed and the survival in this cohort is even lower at 65% (31). The severity of the defect can be measured prenatally by the degree of pulmonary hypoplasia and the survival drops to below 30% for those with expected lung volumes below 30% of expected (7, 32).

The purpose of the FETO procedure in severe CDH patients is to improve prenatal lung growth in order to potentially increase neonatal survival. This procedure is currently being offered at selected fetal centers in the United States. The Fetal Diagnosis and Treatment Center (FDTC) at Michigan Medicine has been offering a range of fetal interventions since 2006, including open fetal surgery, fetoscopic fetal surgery, and fetal cardiac valvuloplasty and septostomy. The skill set needed to perform FETO is present with our mature team at Michigan Medicine. Patients are requesting consideration of this experimental treatment with increasing frequency when diagnosed with CDH prenatally. The FDTC team desires to be able to offer this procedure to patients that meet criteria.

The balloon will be placed between 27 weeks 0 days and 29 weeks 6 days and remains in the fetal airway until removal or puncture. The timing for removal or puncture will ideally be between 34 weeks 0 days $\pm$ 1 week and ultimately decided upon by the FDTC Team. This is the current timing based on prior data and is the current timing being used for balloon placement and retrieval in protocols at other centers (33). This timing optimizes lung growth in the late canalicular and early saccular phases and removes/punctures

the balloon prior to delivery in order to avoid need for tracheoscopic removal on placental bypass or emergent neonatal removal (21).

4.4 END OF STUDY DEFINITION

The mother is considered to have completed the study if she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), **Section 1.3**. This will be at completion of the post-partum visit. Standard post-delivery care will be offered to all participants.

For the infants, the end of the study is defined as hospital discharge or 180 days of life if still hospitalized. Neonates will receive the standard therapy for CDH and this is unaffected by the FETO intervention.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability (meets psychosocial criteria below) for the duration of the study
3. Pregnant women, age 18 years and older
4. Singleton pregnancy
5. No pathogenic variants on microarray or pathologic findings on karyotype
6. Fetal echocardiogram with changes expected with CDH and no major structural cardiac defects
7. Fetal CDH (left or right) with severe pulmonary hypoplasia, defined as o/e LHR <25% with liver up
8. Gestational age at FETO procedure: if o/e LHR <25%, will be done at 27 weeks plus 0 days to 29 weeks plus 6 days
9. Meets psychosocial criteria
    - Willing to reside within 30 minutes of Von Voigtlander Women's Hospital and ability to maintain follow up appointments
    - Patient has a support person (e.g. spouse, partner, friend, parent) that is available to stay with her for the duration of the pregnancy near Von Voigtlander Women's Hospital
    - Willing to comply with restrictions of daily living including inability to exercise, have intercourse, or return to work

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Multi-fetal pregnancy
2. History of latex allergy
3. History of preterm labor or incompetent cervix (requiring cerclage), short cervix ($\leq$20mm), or uterine anomaly predisposing to preterm labor

4. Psychosocial ineligibility
    - Inability to reside within 30 minutes of Von Voigtlander Women's Hospital or inability to maintain follow up appointments
    - Social work will meet with each patient to evaluate the social situation and support system. Identifiable issues of social instability or compliance with the protocol will exclude her as a potential candidate (see **Section 5.3** for specifics).
5. Bilateral CDH, unilateral CDH with o/e LHR $\geq$ 25%, or unilateral CDH with o/e LHR <25% but liver completely down in abdomen
6. Additional fetal or genetic abnormalities that would impact care after delivery or be known to have an impact on outcome
7. Maternal contraindications to elective fetoscopic surgery
8. Significant placental abnormalities (abruption, chorioangioma, accreta) known at time of enrollment and/or surgery
9. Maternal isoimmunization or neonatal alloimmune thrombocytopenia
10. Maternal HIV, Hepatitis B with positive surface antigen, Hepatitis C with presence of virus in maternal blood due to risk of fetal transmission during the procedure
11. No safe or feasible fetoscopic approach to balloon placement

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Reside within 30 minutes of Von Voigtlander Women's Hospital and C.S. Mott Children's Hospital
- Maintain weekly follow up appointments while the balloon is in place and up until delivery
- Have a support person (e.g. spouse, partner, friend, parent) that is available to stay with her for the duration of the pregnancy and attend weekly appointments
- Would be unable to carry on normal daily activities including exercise and intercourse. Would not be able to work for the remainder of pregnancy after the balloon placement.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to be evaluated for the clinical trial but do not meet inclusion and/or exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of psychosocial ineligibity such as inability to reside within 30 minutes of Von Voigtlander Women's Hospital or inability to maintain follow up appointments may be rescreened if their situation changes. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

- We plan to enroll pregnant women age 18 years or older until 10 balloon placements occur, race or ethnicity are not inclusion or exclusion criteria. We expect that as many as 100 pregnant women will need to be screened in order to meet our target enrollment of 10 women.
- We expect accrual of 10 patients to take approximately 48-60 months.
- Single Site: Fetal Diagnosis and Treatment Center (FDTC) at Michigan Medicine
- Source of participants: Patients presenting to the FDTC for prenatal diagnosis and counseling. Some may be initially diagnosed by the investigators in this study but a majority are expected to be from outside referrals due to the increasing interest in this procedure and our current status as a referral institution for CDH in the region.
- How potential participants will be identified and approached: Pregnant women carrying fetuses with prenatally diagnosed CDH will be identified during prenatal diagnosis and counseling. Those who potentially meet inclusion criteria will be offered potential enrollment.
- Types of recruitment strategies planned: FDTC website with details of the study, mailers to referring physicians with information regarding the trial, and social media outlets will be used to raise awareness of the trial.
- CDH is thought to be a sporadic anomaly of development but is more common in Caucasians. Although all pregnant women carrying a fetus with CDH will be screened for inclusion, we expect that a majority of participants will be Caucasian. No racial group will be excluded from screening and all eligible persons will be recruited for the study independent of race.
- Since this study involves fetal therapy for treatment of fetuses with CDH, recruitment of pregnant women is mandatory. In order to safeguard this vulnerable population, all women will be counseled similarly and without coercion. At least 2 separate investigators will discuss the risks and benefits of the procedure with the patient and any support people she desires. Additionally, we will require a minimum of 24 hours of contemplation after initial counseling prior to signing consent. In addition to counseling by two separate providers, we will have social work assess the patient and any support persons to evaluate for evidence of coercion or lack of understanding of the procedure or the implications.
- It would be a rare case for a pregnant woman carrying a fetus with CDH to also be incarcerated. This patient would be seen in the FDTC and screened for inclusion. Prisoner status will not exclude her from entering the trial but she would have to pass the social screening and be in a position to be compliant with the protocol at the time of balloon placement. These cases will be handled on a case by case basis.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S)

6.1.1 STUDY INTERVENTION DESCRIPTION

Intended Use:
The Fetal Endoscopic Tracheal Occlusion (FETO) procedure using the Goldballoon Detachable Balloon (GOLDBAL2) along with the Delivery Microcatheter (BALTACCI-BDPE100) is being investigated to treat fetuses with severe Congenital Diaphragmatic Hernia (CDH).

FETO Procedure description:
The procedure for deployment of fetal tracheal balloon will take place between 27 weeks 0 days and 29

weeks 6 days' gestation as per protocol above. Balloon retrieval or puncture will ideally take place between 34 weeks 0 days ± 1 week. Specifics related to the procedure are in **Section 6.1.2.**

Device Descriptions:
General Fetoscopic Equipment:

- Karl Storz Trocar (11650 TG) for uterine access and introduction of cannula (K943713)
- Cook Cannula RCF-10.0 Check-Flo Performer Set (K142829)

Device and components for balloon placement:

- Karl Storz Fetal tracheoscopic sheath with 3 side ports (11540 KE)
- Karl Storz Fetal tracheoscope (11540 AA) (K951343)
- BALT Goldballoon Detachable Balloon (GOLDBAL2)
- BALT Delivery Microcatheter (BALTACCI-BDPE100)

Device and components for balloon retrieval/puncture:

- Karl Storz Fetal tracheoscopic sheath with 3 side ports (11540 KE)
- Karl Storz Fetal tracheoscope (11540 AA) (K951343)
- Karl Storz Retrieval forceps (11510 C) (K951343)
- Karl Storz Puncture Needle (11540 KD)
- Karl Storz Disposable Puncture Needle (11506 P)

6.1.2 DESCRIPTION OF FETO PROCEDURE

The procedure for deployment of fetal tracheal balloon will take place between 27 weeks 0 days and 29 weeks 6 days' gestation as per protocol above. After adequate counseling and signed informed consent, the pregnant mother will come with her support person on the day of surgery. She will be admitted to the hospital and, after confirmation of fetal viability, she will have either an epidural placed by anesthesia providers or maternal IV sedation with local anesthesia, depending upon the patient wishes and care team assessment. Once in the operating room and positioned, ultrasound assessment for fetal positioning will be confirmed. Maternal indomethacin will be administered in the operating room or prior to entry into the operating room based on maternal preference. When fetal positioning is appropriate, the fetus will receive an intramuscular injection of fentanyl (15 μg/kg), atropine (20 μg/kg), and vecuronium (0.2 mg/kg) (dose based on estimated fetal weight) as provided by fetal anesthesia. The fetal medications will be redosed as needed during the procedure to ensure minimal fetal movement and adequate fetal anesthesia. If an epidural is used for the procedure, supplementation with maternal IV sedation may also be used. After adequate maternal anesthesia, a 10F vascular sheath would be inserted into the uterus using a Seldinger technique. The fetal tracheoscope will be inserted into the fetus' mouth and the balloon will be deployed once in correct position in the fetal trachea. The balloon will be inflated with 0.6 – 0.8 ml of isotonic fluid and detached into the fetal trachea. This will complete the placement portion and the fetoscope will be withdrawn. Ultrasound verification of the balloon placement above the carina will be done prior to procedure completion. Amnioreduction will be done if required and the uterine trocar will be removed. The skin will be closed with an absorbable suture and/or surgical skin glue.

Balloon placement attempt will be defined as trocar placement into the uterus with attempt to gain access into the fetal trachea. We will allow a single uterine trocar placement for each patient for attempted initial placement. If our team fails to place the balloon (surgical failure), this will not be attempted a second time. However, if the balloon is successfully placed and later deflates or is expelled from the fetal trachea (balloon failure), a second attempt will be allowed to maximize benefit to the fetus if this occurs within 10 days of initial insertion and this timing is up to and including 29 weeks and 6 days' gestation.

Therefore, a maximum number of balloon placement attempts are: 1 for cases of surgical failure and 2 for cases of balloon failure. There may be cases where the patient is taken to the operating room and, due to suboptimal fetal positioning, uterine access is not attempted. Attempts will be made to externally rotate the fetus into position however if on ultrasound the fetus remains in poor position for balloon placement, uterine access will not proceed. This will not count as a placement attempt and the patient would return to the operating room on subsequent days an unlimited number of times up to 29 weeks and 6 days with the goal of uterine access.

Balloon retrieval or puncture will ideally take place between 34 weeks 0 days $\pm$ 1 week. This may occur earlier in select cases for maternal or fetal indications for delivery (see **Section 6.5.1** for more specific details). The pregnant mother may again have an epidural placed or maternal IV sedation with local anesthesia, depending upon patient wishes and care team assessment. Maternal IV sedation may be given if deemed necessary to supplement the epidural. Once in the operating room and positioned, the fetus will receive an intramuscular injection of fentanyl, atropine, and vecuronium (dose based on estimated fetal weight). Redosing will be done as needed during the procedure to ensure minimal fetal movement. A 10F vascular sheath would be inserted into the uterus using a Seldinger technique. The fetal tracheoscope will be inserted into the fetus' mouth and the balloon will be punctured and retrieved from the fetal trachea. Amnioreduction will be done if required and the uterine trocar will be removed. The skin will be closed with an absorbable suture and/or surgical skin glue. In select cases where fetoscopic intervention is deemed higher risk (e.g. chorioamniotic membrane separation, symptomatic polyhydramnios with premature contractions, or preterm labor), attempts may be made to puncture the balloon under ultrasound guidance in order to avoid trocar placement into the uterus. The reason for utilizing the percutaneous route secondarily is that the needle decompression is done via ultrasound guidance and not direct visualization. With the percutaneous approach, the needle passes through the fetal neck risking injury to vital structures (carotid artery, internal jugular vein, nerves, etc.). Also, the balloon is not removed and depends on fetal expulsion from the trachea without assurance that balloon remnants do not remain in the fetal airway. Since the balloon is not physically removed after a intrauterine ultrasound-guided balloon puncture, there is a potential that the balloon remains inflated in the fetus's airway after attempted puncture. Another fetal MRI will be performed following intrauterine ultrasound-guided balloon puncture in clinically stable patients to confirm deflation. If the balloon is unable to be retrieved or punctured prior to delivery, tracheoscopic removal or puncture on placental bypass during standard Cesarean section or an EXIT procedure will be planned for safe removal of the balloon prior to birth. In the case of a precipitous vaginal delivery tracheoscopic removal on placental bypass may occur after vaginal delivery and before placental delivery. These decisions will be made by members of the FDTC team with a multi-disciplinary approach after thorough discussion about what is safest for both mom and baby. Potential scenarios requiring tracheoscopic removal on placental bypass include failure to remove the balloon under other usual means or preterm labor with eminent delivery and inability to remove the balloon by fetoscopic or percutaneous approaches. Unless the balloon remnant is physically removed, emergency bronchoscopy equipment will remain available in our Neonatal Emergency Stabilization and Treatment (NEST) area until delivery and the pediatric surgery, emergency airway, and neonatology teams will be trained in neonatal balloon puncture with or without removal.

After each intervention, subjects will be admitted post-operatively for observation, pain control, and continuous uterine monitoring for contractions. Indomethacin (100mg per rectum preoperatively and then 50mg every 6 hours for 24 hours) will be given with the first fetoscopy to mitigate risk of premature contractions. Prophylactic preoperative antibiotics will also be administered intravenously to mother at both balloon placement and retrieval to minimize infectious risk (cefazolin 2 grams is preferred; allergies may require appropriate substitutions). Maternal pain control will include Tylenol as needed with narcotic medications reserved for breakthrough pain. Nifedipine (10-20mg every 8 hours or 30mg extended release daily as tolerated) may also be given postoperatively to reduce uterine irritability. Length of postoperative stay will be individualized to the patient but is expected to be a 1 night stay for the majority

of patients. Upon discharge, the mother and fetus will be followed on an out-patient basis as further described in **Schedule of Activities (section 1.3)**. While the balloon is in place, mothers will be followed at least weekly with an interval history, interval exam, and fetal ultrasound as per standard of care. The ultrasound will assess for fetal growth, amniotic fluid volume, LHR, o/e LHR, and balloon visualization (when balloon is in place). After balloon removal/puncture, mothers will be monitored weekly for sign of labor. Route of delivery will be based on obstetric indications with vaginal delivery being the preferred approach.

6.2 DEVICE ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Goldballoon Detachable Balloon (GOLDBAL2) along with the Delivery Microcatheter (BALTACCIBMPE100) will be provided by the manufacturer, Balt Extrusion (Montmorency, France). It will be opened under sterile conditions at the time of procedure.

All use of the Goldballoon Detachable Balloon (GOLDBAL2*)* will be under the direct supervision of the principal investigator or her designee. The investigational devices will be clearly labeled as investigational use only. The devices will be stored in the office of the Surgical Care Coordinator in the FDTC at Michigan Medicine, with access limited to the study team.

All records of receipt, use, and disposition of the devices will be maintained by the study team. At the completion of the study, there will be a final reconciliation by study personnel of devices shipped, used, and devices remaining. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused devices.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a non-randomized pilot feasibility trial, and as such, all enrolled participants will undergo the same procedures as per the SOA (**Section 1.3**).

6.4 STUDY INTERVENTION COMPLIANCE

Enrolled participants will be expected to reside within 30 minutes of Von Voigtlander Women's Hospital for the remainder of the pregnancy. They will be expected to maintain weekly follow up appointments while the balloon is in place and until delivery. At each visit, an ultrasound will be done to assess for balloon visualization, amniotic fluid volume, and observed-to-expected lung to head ratios (o/e LHRs) as well as overall status of the fetus. Women will need to have a support person (e.g. spouse, partner, friend, parent) that is available to stay with her during the duration of the pregnancy and to follow up visits. She will be unable to carry on normal daily activities including exercise and intercourse and would be unable to return to work after the balloon was placed until after delivery. Compliance to study restrictions will be assessed at each visit via discussion with patient and her support person. We will then document these responses on an electronic Case Report Form (eCRF).

6.5 CONCOMITANT THERAPY

For this protocol, no outpatient medications will be started or stopped due to the intervention. All women will receive indomethacin at the time of initial procedure and during the initial postoperative hospital stay

to minimize risks of preterm delivery. All women will receive a course of antenatal betamethasone (12mg intramuscularly every 24 hours for 2 doses) to promote fetal lung development prior to balloon retrieval/puncture due to the known risk of preterm delivery. If tolerated, they may be maintained on nifedipine after balloon placement to decrease uterine irritability. The remainder of the obstetric care would include medications that would be administered independent of enrollment in this feasibility trial. These medications would include magnesium sulfate if delivery is thought imminent prior to 32 weeks gestation as per standard of care.

6.5.1 RESCUE MEDICINE

Polyhydramnios is expected while the balloon is in place due to the occlusion of the fetal trachea. If polyhydramnios causes symptoms of respiratory distress or preterm contractions in the mother or if the polyhydramnios is progressive, the FDTC team would evaluate for an amnioreduction in order to improve the outcome. If preterm labor were to occur, steroids (as per **section 6.5**) will be administered, if not previously given, with consideration of tocolysis with or without amnioreduction if indicated. If preterm, premature rupture of membranes (PPROM) occurs, hospitalization for the remainder of pregnancy would be recommended and antibiotics would be considered for prolongation of latency period. There are cases where the balloon would need to be removed/punctured prior to scheduled removal/puncture at 34 weeks $\pm$ 1 week. Cases will each be evaluated on an individual basis but scenarios that are most likely to require premature removal/puncture are related to imminent delivery. Maternal reasons for imminent delivery would include medical complications of pregnancy (e.g. pre-eclampsia with severe features or preterm labor not responsive to treatment). Fetal reasons for imminent delivery may include fetal distress. Finally, symptomatic polyhydramnios that is not responsive to amnioreduction or unable to be treated with amnioreduction may be an indication for early balloon removal/puncture.

In the extremely rare case of inability to remove the balloon and need for urgent delivery, the FDTC team would plan tracheoscopic removal on placental bypass during standard Cesarean section or an ex-utero intrapartum therapy (EXIT) procedure for safe delivery of the fetus. This procedure involves a maternal hysterotomy under either regional or general anesthesia with partial delivery of the fetal head and neck. The fetus remains on placental circulation for oxygenation and the balloon will be removed/punctured prior to full delivery and removal of the fetus from placental bypass. The FDTC team has experience with this procedure. If tracheoscopic removal/puncture on placental bypass was unable to be completed, an emergency airway team is available at all times at C.S. Mott Children's Hospital. Emergency bronchoscopy equipment will be available in our Neonatal Emergency Stabilization and Treatment (NEST) area and the emergency airway team will be trained in neonatal balloon puncture with or without removal. Emergent neonatal balloon puncture with or without removal will be completed using real time video-endoscopy to remove the balloon, and if able to at the time, any balloon fragments, suction and clear the airways, and intubate to start ventilation while the cord remains attached to the placenta (e.g. if precipitous vaginal delivery). The emergency airway team will be taught that if the endoscope is in contact with the inflated balloon, the mucosa may appear flattened and the trachea is being stretched. This will require slight retraction of the endoscope to avoid tracheal injury and allow for balloon decompression and possible removal. Intent will be for delay of the cord clamping until signs of open and functional airways are present.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If the balloon is removed/punctured prior to the scheduled 34 weeks ± 1 week for maternal or fetal reasons, the balloon will not be replaced and the patient will continue to be followed per study protocol (see **Schedule of Activities, section 1.3**). This is not considered a protocol deviation when removal is instigated by a maternal or fetal reason other than maternal desire to withdraw from the study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. If requested, the balloon will be removed prior to scheduled removal/puncture at 34 weeks ± 1 week. The balloon may also be removed/punctured prior to 34 weeks ± 1 week if there are maternal or fetal concerns that arise. If the balloon is removed/punctured early for maternal or fetal risk reasons, this will not be considered a withdrawal of participation but will be listed as an adverse event.

In the unlikely case that a mother decides to withdraw from the study after balloon placement and before scheduled removal/puncture, the FDTC team would follow the wishes of the patient after extensive counseling. She would still require weekly OB/MFM follow-up to ensure safe delivery and we would recommend delivery in a CDH center as per standard of care. Although not advised, if she decided to deliver at another institution we would take the steps necessary to discuss with the delivery team and pediatric surgery team at the accepting center regarding what had been done and what potential complications should be evaluated for due to the fetal intervention. In this case, the participant will not be replaced. Data from the withdrawn patient will be collected but not analyzed in the final analysis.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Fetal distress (e.g. sustained fetal heart rate changes) which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation prior to balloon placement
- Participant unable to have the balloon placed by 29 weeks and 6 days.

The reason for participant discontinuation or withdrawal from the study will be recorded on the electronic Case Report Form (eCRF). Subjects who sign the informed consent form and are enrolled but do not have the balloon placed may be replaced. Subjects who sign the informed consent form, are enrolled and have the balloon placed, but subsequently withdraw or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- In the rare case that the mother is completely lost to follow-up, the study team will contact her referring physician as there is potential for infant risk if the balloon is in place and not retrieved/punctured prior to birth or immediately after birth. Instructions on how to retrieve/puncture the balloon postnatally will be provided to her home obstetrician.
- All mothers will be given a wallet-sized emergency card with information regarding the balloon and what is to be done in an emergency situation.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING AND STUDY PROCEDURES

Candidates for the trial will be identified from the investigator's clinic practice or may be referred from other clinicians. All screening examination procedures will be performed by the investigator or trained personnel working under the investigator's supervision.

Screening

- Maternal demographics
- Inclusion/Exclusion criteria reviewed

Please refer to the Schedule of Activities (SoA), **section 1.3** of the protocol for standard of care activities that will be performed or obtained from the patients' medical record in order to determine eligibility and obtain baseline data.

The following screening examination and procedures will be completed during the screening period as per standard of care for women carrying a fetus diagnosed with CDH:

- Maternal medical history and physical exam
- Maternal vital signs (temp, pulse, respirations, blood pressure), height and weight
- Maternal clinical laboratory tests, including complete blood count, blood type and screen, antibody screen, HIV, Hepatitis B, and Hepatitis C
- Fetal karyotype or microarray
- Confirmation of CDH diagnosis with comprehensive US including observed to expected Lung to Head ratio (o/e LHR)
- Fetal Echocardiogram
- Fetal MRI with calculated observed to expected total fetal lung volume (o/e TFLV)

- Extensive counseling with multidisciplinary team
- Maternal screening for substance abuse and depression (using the Edinburg Postnatal Depression Scale)

Patients who meet all enrollment criteria and who, after receiving appropriate study information, provide their informed consent (as evidenced by a signed informed consent document), will be enrolled in the study and have the FETO procedure for balloon placement performed at 27+0 to 29+6 weeks gestation per section 6.1.2.

Follow up procedures will occur as listed in **section 1.3 Schedule of Activities** table.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All adverse events will be recorded on eCRFs. The description of the event, date first observed, any action taken, and ultimate outcome will be recorded.

For all adverse events, sufficient information will be pursued and/or obtained so as to permit
1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and;
2) an assessment of the causal relationship between the adverse event and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse events felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

The investigator will classify all adverse events as expected or unexpected, and as either not related to the investigational device or surgical procedure, unlikely related to the investigational device or surgical procedure, potentially related to the investigational device or surgical procedure, probably related to the investigational device or surgical procedure, or definitely related to the investigational device or surgical procedure.

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any undesirable occurrence in a study patient, whether or not it is related to the study intervention. Any condition that was recorded as pre-existing is not an AE unless there is a change in the nature, severity, or degree of the condition.

Adverse events will be recorded on the appropriate event eCRF. The date of the event, seriousness criteria, relatedness, expectedness and outcome will also be recorded. Adverse events will be collected once the participant has been enrolled in the trial and the subject will be instructed to report any event to the Investigator when and/or as it occurs. Adverse events will be collected for mother up until the time of her postpartum visit. Adverse events for the fetus/baby will be collected for 30 days after delivery.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, an unanticipated life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization of mother,

or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions after delivery. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible. The event must be phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time of the study intervention, is unlikely to be attributed to concurrent disease or other procedures, other drugs or chemicals.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "potentially related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to the study intervention makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after the study intervention) and in which other procedures, other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention, and/or evidence exists

that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3.3 EXPECTEDNESS

The study investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

AEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. If the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All reportable events will be recorded with start dates occurring any time after informed consent is obtained until the post-partum visit for the mom and 30 days after delivery for the baby. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Clinical Events Committee (CEC) will adjudicate all serious or related (potentially, probably or definitely) adverse events for clinical accuracy and relatedness to the treatment, and will also ensure a unified evaluation by applying standardized event criteria. The CEC will perform final adjudication of adverse events.

8.2.5 ADVERSE EVENT REPORTING

All adverse events that occur will be assessed for expectedness and relatedness. Adverse events will be reported to the University of Michigan IRBMED in accordance with their policy.

Infant adverse events associated with CDH and expected as normal course of the condition will be recorded as expected. Such events include but are not limited to:

- Death after birth due to CDH disease severity and/or complications of standard of care treatment
- Pulmonary hypertension with resultant need for medications or need of ECMO
- All complications associated with ECMO (i.e. bleeding, stroke, etc.)

- Pulmonary hypoplasia with resultant need for mechanical ventilation
- Gastrointestinal reflux or other feeding problems (i.e. dysmotility, need for feeding tube, etc.)
- Increased oxygenation requirements or need for home oxygen
- Neurodevelopmental delay

8.2.6 SERIOUS ADVERSE EVENT REPORTING

An adverse event is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Maternal death and/or fetal death
    - If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event

An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for > 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect other than those expected of a baby with CDH
- Important medical event

Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions (e.g. CDH in infant) that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.7 UNANTICIPATED ADVERSE DEVICE EFFECTS

An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects."

All serious and unanticipated adverse events should be reported to the sponsor investigator within 24 hours of first learning of the event. Those that are determined to be serious and unanticipated after sponsor investigator review should also be reported to the IRB as required according to the reporting requirements of the University of Michigan IRBMED.

The Sponsor-Investigator will work with the University of Michigan Institute of Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program to report all UADEs to the Food and Drug Administration (FDA) within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor investigator shall submit such additional reports concerning the effect as FDA requests. The sponsor investigator shall also report the results of such evaluation to the University of Michigan IRB in the expected time frame of the institution's IRB policy.

All UADEs will be reported to the IRB according to local policies and to the FDA according the regulations found in 21 CFR 812.150.

8.2.8 POST-DELIVERY REPORTING

Within 30 days of delivery for subject enrolled in the study who had a balloon placed, we will provide a post-delivery report to the FDA. In addition, we will also provide the FDA a report of any neonatal/infant death not determined to be associated with the FETO procedure (i.e. due to postnatal complications).

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB HUM number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported to University of Michigan IRBMED in accordance with their policy.

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The screening data for all subjects who are screened, but do not meet eligibility criteria, will not be analyzed or tabulated nor collected on the eCRFs. The reason for screen failure will be captured on the eCRFs.

All participants that have balloon placement will be analyzed with descriptive statistics except for the unlikely voluntary withdrawal from the study. The number of subjects included in the safety and/or effectiveness evaluations, subjects completing the study, and the reasons for any withdrawals will be tabulated by counts and percentages. Continuous demographic data will be summarized using descriptive statistics. Categorical demographic data will be summarized using counts and percentages. Abnormal medical histories, ocular histories, and prior/concurrent medications obtained on the screening visit will be presented in data line listings.

9.2 STATISTICAL ANALYSES

9.2.1 SAMPLE SIZE

This pilot study sample will include 10 patients who successfully undergo balloon placement. We may need to enroll additional patients in the case of screen failures and those that have failed balloon placement due to fetal positioning. As this is a pilot study, a sample size calculation will not be performed.

9.2.2 GENERAL STATISTICAL CONSIDERATIONS

Descriptive tabular and graphical summaries of data will be used to characterize primary and secondary endpoints. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, median, minimum and maximum values will be reported.

9.2.3 SAFETY ANALYSES

As this is a pilot study with a very small number of planned subjects, there will be no internal statistical analysis of safety. Analyses will include descriptive statistics on all safety measures (expected and unexpected complications) and adverse events.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INSTITUTIONAL REVIEW BOARD

This protocol and the ICF will be approved initially and reviewed annually by the University of Michigan Institutional Review Board (IRB). Progress reports will be submitted at the completion of the study or at least once yearly, whichever comes first, to the IRB. Serious adverse events will be reported to the IRB and the FDA in accordance with applicable FDA regulations for serious adverse events.

10.1.2 INFORMED CONSENT PROCESS

In accordance with the provision of 21 CFR Part 50, each subject will provide written informed consent for participation in this study prior to the use of the investigational device.

The study will be explained to the prospective subject by the investigator or her designee. The nature of the experimental product will be explained together with potential hazards of the surgical procedure, including any possible adverse reactions. The subject will be informed that she is free to terminate participation in the study for any reason. One copy of the signed consent form will be retained in the medical record and one copy will be given to the subject.

10.1.2.1 CONSENT PROCEDURES AND DOCUMENTATION

In accordance with the provision of 21 CFR Part 50, each subject will provide written informed consent for participation in this study prior to the use of the investigational device.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.3 KEY ROLES AND STUDY GOVERNANCE

Co-Principal Investigators	
Erin Perrone, MD, *Associate Professor* *Pediatric Surgery*	*Caitlin Clifford, MD* *Assistant Professor* *Obstetrics & Gynecology, Maternal Fetal Medicine*
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10.1.4 SAFETY OVERSIGHT

To protect the interests of research subjects and ensure that they are not exposed to undue risk, this trial will be monitored by an independent Data and Safety Monitoring Committee (DSMC). The DSMC will been appointed by the Sponsor-Investigator, and shall have no formal involvement with the subjects or the investigation and function independently of Sponsor-Investigator. The DSMC will be composed of physicians from the following specialties: pediatric surgery, maternal fetal medicine, neonatology, and pediatric pulmonology, independent of the sponsor-investigator and co-investigators.

The DSMC will monitor the progress of the trial with a scheduled meeting or conference call. In addition to reviewing Serious Adverse Events (SAEs), the first DSMC meeting will focus on over all safety of the trial and study device and will make a determination as to whether or not the study should proceed.

The DSMC will also serve as the Clinical Events Committee (CEC), and will adjudicate all adverse events for clinical accuracy and relatedness to the treatment, and will also ensure a unified evaluation by applying standardized event criteria. The CEC will perform final adjudication of adverse events.

If any of the following study stopping rules are met, the study team will voluntarily suspend the study pending review by the DSMC. The FDA will be notified immediately of a halt to study enrollment and FDA approval will be obtained prior to resuming enrollment.

Study stopping rules:

- Single maternal death
- Fetal death associated with balloon insertion/removal procedures
- Technical failure in 50% of cases

10.1.5 CLINICAL MONITORING

To assure adequate protection of the rights of human subjects, per 21 CFR §812.40, 812.43 and 812.46, this study will be monitored by the University of Michigan Institute of Clinical and Health Research (MICHR). Routine monitoring will be scheduled at appropriate intervals, with more frequent visits occurring at the beginning of the study as per the monitoring plan. A site activation visit will take place, followed by routine monitoring visits. Additional visits can be scheduled at the request of the Sponsor-Investigator. The established monitoring plan will ensure the quality and integrity of the data throughout the study conduct to verify adherence to the protocol, completeness and accuracy of study data and samples collected, dispensing and inventory of the device, and compliance with regulations.

10.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Adequate records will be maintained for the study including subject medical and surgical records, signed ICFs, and device use records. All original source documentation will remain at the investigative site. Study data that are stored at the investigator site in any electronic medical records system, including measurements that are obtained electronically, will be retained in the study files.

A secure, regulatory-compliant, web-based electronic data capture (EDC) system designed specifically for investigators and their research teams will be used for data collection and management. The EDC is built on a flexible and extensible data model that can accommodate input of diverse clinical or laboratory data. The system possesses the ability to maintain an audit trail of the entire study, enabling traceability of entries and modifications to research-related data. Role-based access to the application, the databases

and archives, and the underlying systems infrastructure comply with industry best practices and meet HIPAA security and privacy requirements, governed by HIPAA's "minimum necessary" principle."

10.1.6 PROTOCOL DEVIATIONS

The investigator will not deviate from the protocol without prior IRB and sponsor investigator approval, unless such deviation is necessary to manage a medical emergency. The investigator will notify the IRB and the sponsor investigator of any protocol deviation to protect the life, or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event any later than 5 working days after the emergency occurred. All other revisions and/or amendments to the protocol that affect subject treatment, study outcome, or subject safety should be submitted in writing to the IRB for approval prior to implementation. The investigator should maintain a record of all protocol deviations showing the dates of, and the reason for, each protocol deviation.

Changes that affect the scientific soundness of the study or the rights, safety, or welfare of human subjects may also require FDA approval, in addition to IRB approval, prior to implementation. The sponsor investigator will obtain such approvals, if required.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CDH	Congenital Diaphragmatic Hernia
CFR	Code of Federal Regulations
CGC	Certified Genetic Counselor
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMC	Data Safety Monitoring Committee
DRE	Disease-Related Event
EC	Ethics Committee
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Forms
EPDS	Edinburg Postnatal Depression Scale
EXIT	Ex-Utero Intrapartum Therapy
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDTC	Fetal Diagnosis and Treatment Center
FETO	Fetal Endoscopic Tracheal Occlusion
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices

GWAS	Genome-Wide Association Studies
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LHR	Lung to Head Ratio
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MFM	Maternal Fetal Medicine
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NEST	Neonatal Emergency Stabilization and Treatment
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PPROM	Preterm Premature Rupture of Membranes
PROM	Premature Rupture of Membranes
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
5.0	24 July 2020	Added tracheoscopic removal on placental bypass during standard Cesarean section	May be needed for balloon removal
6.0	9 April 2021	Changed balloon fill volume from 0.6 ml to 0.6-0.8 ml	Option to have the balloon filled to 0.8 ml
7.0	21 June 2021	Added tracheoscopic removal on placental bypass during precipitous vaginal delivery and balloon migration to the risks section	We had experience with both precipitous vaginal delivery and balloon migration out of the trachea and was swallowed by the fetus/neonate. Although both rare events, we added to the protocol and informed consent.
8.0	16 February 2022	Changed maternal follow up visit window from 4-6 weeks to 4-8 weeks	This will allow those who live farther away more time to make their appointment, and allows for more time if appointment gets rescheduled.
9.0	23 February 2023	Added nifedipine as an option to be given to decrease the risk of uterine irritability and also amnioreduction even without symptoms if it is progressive. Also added the potential to do the procedure without epidural and utilizing maternal sedation and local anesthesia as determined by the care team. Also added members to our fetal team (Drs. Davis & Clifford) and deleted a member (Dr. Carver) which is reflected in this version. Added “chorioamniotic membrane separation” as a known complication and, when present, likely need to do intrauterine guided balloon puncture as opposed to fetoscopic retrieval	These are all additions to the protocol after discussion with other fetal surgeons around the country. Amnioreduction and nifedipine have been theorized to decrease preterm delivery. Additionally, other centers are avoiding epidural for the placement and retrieval, and we want that option to be available for our team as well. We have had change in our fetal team with 2 new members and 1 leaving for another position. Chorioamniotic membrane separation was identified in 22-26% of patient in the TOTAL trials (severe and moderate arms). This makes fetoscopic

		Added “Balloon remnants, or intact/inflated balloon, remaining in the airway, potentially requiring additional evaluations to monitor location and/or procedures to remove if it causes obstruction or any other complications from retention versus observation” to the potential risks and added “balloon puncture with or without removal” to the description of the procedure and added puncture to mentions of retrieval throughout protocol Added additional MRIs as needed	attempts challenging and potentially impossible. Due to an airway injury after repeated attempts at removal of a balloon remnant, our team reached out to other centers that described leaving the remnant in the airway in a minority of cases without known sequelae. We also reached out to Dr. Jan Deprest (lead investigator in the TOTAL trial) who reports 15/287 (5%) of FETO cases where the metallic component of the balloon remained in the airway without known complications. With this knowledge, our team will attempt at removing the remnant balloon if retained via a single attempt but will avoid repeated attempts due to potential more harm. Some patients may need additional MRIs for clinical or research purposes
9.0	22 January 2024	Personnel Changes	Co-Investigator list updated
10.0	27 February 2024	Added MRI after intrauterine ultrasound-guided balloon puncture	Fetal MRI will be performed following intrauterine ultrasound-guided balloon puncture in clinically stable patients to confirm deflation.
11.0	16 May 2024	Added Dr. Greco	Added Dr. Greco
12.0	23 June 2025	Added post-delivery reporting to the FDA Added study stopping rules Changed co-principal investigator to Dr. Clifford	Added at the request of the FDA following annual repot review. Also, changed co-principal investigator to Dr. Clifford, and kept Dr. Treadwell as co-investigator.

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