Title:	**Pilot Trial of Fetoscopic Endoluminal Tracheal Occlusion (FETO) in Severe Left Congenital Diaphragmatic Hernia (CDH)**
Short Title:	Pilot Trial FETO for CDH
Device Names(s):	GOLDBALLOON: GoldBAL2 Detachable Balloon BALTACCIBDPE100: Catheter System
FDA IDE:	G140236
NCT Number:	02549820
Regulatory Sponsor:	Children's Hospital of Philadelphia
eIRB Number:	15-011714
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Abbreviations and Definitions of Terms

AE	Adverse event
AFI	Amniotic Fluid Index
BDI-II	Beck Depression Inventory II
CDH	Congenital Diaphragmatic Hernia
CFDT	Center for Fetal Diagnosis and Treatment
CXR	Chest X-ray
DSMC	Data Safety Monitoring Committee (Fetal Oversight Committee will act as the DSMC)
ECMO	Extracorporeal Membrane Oxygenation
EXIT	Ex Utero Intrapartum Therapy
FDA	Food & Drug Administration
FETO	Fetoscopic Endoluminal Tracheal Occlusion
FISH	Fluorescence In Situ Hybridization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IUGR	Intrauterine Growth Retardation
IVH	Intraventricular Hemorrhage
LHR	Lung to head circumference ratio
LMP	Last Menstrual Period
OAE	Otoacoustic Emission Test
O/E	Observed/Expected
ORCRA	Office of Research Compliance and Regulatory Affairs
PFT	Pulmonary Function Test
PPROM	Preterm Premature Rupture of Membranes
PVL	Periventricular Leukomalacia
U/S	Ultrasound
SAE	Serious Adverse Event
SDU	Special Delivery Unit
SI	Sponsor-Investigator
TO	Tracheal Occlusion
27^0 weeks	27 weeks 0 days gestation - an example of alternate way to write gestational age

PROTOCOL SYNOPSIS

Study Title	**Pilot Trial of Fetoscopic Endoluminal Tracheal Occlusion (FETO) in Fetuses with Severe Left Congenital Diaphragmatic Hernia (CDH)**
Funder	Departmental funds
Clinical Phase	Pilot
Study Rationale	Despite advances in prenatal diagnosis and postnatal therapies, including ECMO, inhaled nitric oxide therapy, and ventilator strategies that minimize ventilator-induced lung injury, morbidity and mortality rates for babies with severe CDH remain high. Between January 2006 and December 2010, we provided prenatal and postnatal care for 64 patients with isolated left CDH. Overall survival was 63% and use of extracorporeal membrane oxygenation (ECMO) was 33%. Observed/expected lung to head circumference ratio (O/E LHR) is a tool validated in 354 fetuses with unilateral isolated CDH evaluated between 18 and 38 weeks gestation. [1] For O/E LHR < 25%, survival was dismal at 1/9 or 11% (CHOP experience, not published). We have updated survival data for 2010-2015 showing 10/29 (34%) in the liver up O/E LHR <25% group and 11/24 (46%) in the liver up O/E LHR 25-<30% group. Since July 2004, we have also prospectively followed all survivors with CDH in an interdisciplinary follow-up program, uncovering striking morbidities in neuromuscular tone and neurodevelopmental status.[2] The rationale for fetal therapy in severe CDH is to restore adequate lung growth for neonatal survival. Prenatal tracheal occlusion obstructs the normal egress of lung fluid during pulmonary development leading to increased lung tissue stretch, increased cell proliferation, and accelerated lung growth. [3] European colleagues have developed foregut endoscopy [4] and techniques to position and remove endoluminal tracheal balloons in utero.[5,6,7] Recently, the Belgium group published summary results of FETO showing an improved survival in 175 patients with isolated left CDH from 24% to 49%.[7] Our goal with this pilot study is to study the feasibility of implementing FETO therapy in fetuses with severe left CDH– (O/E LHR < 25%).
Study Objective(s)	**Primary** • To determine feasibility and safety of performing FETO in fetuses with left CDH with LHR O/E < 25% (Severe CDH).

	Secondary • Demonstrate fetal lung growth due to successful FETO • Determine survival rate and outcome measures of FETO patients
Test Article(s)	The following devices will be used for this study: **BALT GOLDBAL2** – Catheter system (BALT Extrusion, Montmorency, France). A 1.5 mm detachable balloon (**Goldbal 2**) and COAX catheter (**BALTACCIBDPE100**). Balloon is radiopaque which marks the most frontal tip. The balloon is easily identified by ultrasound or MRI due to its echogenicity. The inflating catheter system consists of (1) 9.22 mm inner wire, (2) 1.5F inside tube with a tapered distal tip for mounting the balloon, (3) 3F outer catheter for releasing the balloon and (4) a removable universal base. This is an investigational device.
Study Design	This is an un-blinded non-randomized pilot study.
Subject Population **Key criteria for Inclusion and Exclusion:**	**Inclusion Criteria** 1. Pregnant women age 18 years and older, who are able to consent 2. Singleton pregnancy Fetal: 3. Normal Karyotype or chromosomal microarray with non-pathologic variants 4. Diagnosis of Isolated Left CDH with liver up 5. Gestation at enrollment prior to 29 wks plus 5 days for SEVERE pulmonary hypoplasia with US O/E LHR < 25% **Exclusion Criteria** 1. Pregnant women < 18 years 2. Maternal contraindication to fetoscopic surgery or severe maternal medical condition in pregnancy 3. Technical limitations precluding fetoscopic surgery 4. Rubber latex allergy 5. Preterm labor, cervix shortened (<15 mm at enrollment or within 24 hours of FETO balloon insertion procedure) or

	uterine anomaly strongly predisposing to preterm labor, placenta previa 6. Psychosocial ineligibility, precluding consent 7. Fetal Diaphragmatic hernia: right-sided or bilateral, major associated anomalies, isolated left-sided with the O/E LHR ≥ 25% 8. Inability to remain at FETO site during time period of tracheal occlusion, delivery and postnatal care
Number Of Subjects	25 subjects total. (IDE Approval: G140236)
Study Sites	Single center investigational site (CHOP)
Study Duration	Each child will be followed through a 24 month follow-up visit The entire study is expected to last 7 years. For the purposes of moving on to a randomized multi-centered trial, the study is expected to move forward after the primary objectives related to feasibility and safety through the neonatal period have been met.
Study Phases **Screening** **Study Treatment** **Follow-Up**	Screening for eligibility and obtaining consent Study intervention (FETO & balloon retrieval) Follow-up visits will occur at 6 months, 12 months, and 24 months in the Pulmonary Hypoplasia Clinic at CHOP.
Efficacy Evaluations	Primary evaluation measurements to determine efficacy will include successful completion of surgical procedures, demonstration of lung growth, delivery of live born neonate, survival and long term morbidity.
Safety Evaluations	Safety evaluations will be monitored by adverse events/ serious adverse events, surgical complications and neonatal outcomes.
Statistical And Analytic Plan	Statistics will be descriptive. This is a pilot study to determine feasibility of performing FETO in our institution.
DATA AND SAFETY MONITORING PLAN	Study will be monitored internally by the Office of Research Compliance and Regulatory Affairs. In addition, an external fetal Oversight Committee which will act as the data safety monitoring committee (DSMC) will convene after the first 3 patients enrolled have delivered and babies have been discharged from the hospital or one year, whichever is sooner, to review study results. Fetal Oversight Committee will be consulted at any time if safety concerns arise during the conduct of the research study. Subsequent

	fetal oversight meetings after the initial review of the protocol will be at the discretion of the committee itself.

Table 1: Schedule of Procedures (Screening – Delivery)

Study Phase	**Screening**		**Intervention**			**Delivery**
Visit Number	**1a CFDT Evaluation for CDH (SOC)**	**1b Informed Consent**	**2 Balloon Insertion**	**3 Balloon Insertion to delivery**	**4 Balloon Removal**	**5**
Gestational Age/Chronological Age	18^0-29^5 wks		27^0-29^6 wks	**Weekly Check-ups**	34^0-34^6 wks	37^0-39^0 wks
Demographics/Medical History	X					
Physical Examination	X		X	X	X	
Vital Signs: BP, HR, RR	X		X	X	X	
Height* and Weight	X			X	X	
Patient education including: CDH description, prenatal & neonatal development, general outcomes expected & management options	X					
Prior/Concomitant Medications	X		X	X	X	X
Clinical Laboratory Evaluation (karyotyping, if not previously completed OR microarray)	X		X	X	X	X
Comprehensive Ultrasound: Sonographic Lung Volume with LHR^ Monitoring of amniotic fluid level & membrane status ±	X			X		
Maternal MRI	X			X α		
Fetal Echocardiogram	X			X α		
Psychosocial evaluation	X					
CDH counselling	X					

	Screening	Intervention			Delivery
Visit Number	**1b Informed Consent**	**2 Balloon Insertion**	**3 Balloon Insertion to delivery**	**4 Balloon Removal**	**5**
* **Gestational Age/Chronological Age**	18^0-29^5 wks	27^0-29^6 wks	**Weekly Check-ups**	34^0-34^6 wks	37^0-39^0 wks
Informed Consent	X				
Review Inclusion/Exclusion Criteria with eligible patients	X				
Research Procedures					
Transvaginal Ultrasound	X β				
Clearance for surgery	X			X	
Fetoscopic Tracheal Occlusion		X			
Fetal Growth Surveillance			X¥		
Biophysical Profile beginning at 34 wks (SOC)			X		
Assess Adverse Events/ Serious Adverse Events	X	X	X	X	X
Removal of Balloon				X	
Delivery					X
Beck Depression Inventory (BDI-II)	X				X+

Height performed at initial screening only

^ Serial measurements of sonographic lung volume and LHR will begin within 24-48 hours following surgery and continue weekly by targeted ultrasound evaluation.

± Amniotic fluid level and membrane status will also be monitored at weekly intervals.

β Transvaginal Ultrasound (w/in 24 hours of FETO balloon insertion)

¥ Comprehensive ultrasonography for fetal growth will be performed every four weeks after balloon insertion.

α Targeted Maternal MRI and Fetal ECHO will occur as clinically indicated after balloon insertion until delivery.

+ To be completed within one month of delivery

Table 2: Schedule of Procedures – Follow-up

Study Phase	**Follow-up**			
Visit Number	**6**	**7***	**8***	**9***
Gestational Age/Chronological Age (*Time points based on corrected age)	NICU/Inpt	6 months (+/-1 month)	12 months (+/-1 month)	24 months (+/-1 month)
Echocardiographic assessments[1]	X	X	X	X
Bronchoscopy **(Research Procedure)**	X			
Brain Imaging (Head MRI)[2]	X			
Audiology Examinations	X	X	X	X
Pulmonary Function Testing		X	X	X
Chest Radiograph	X		X	X
Neonatal Follow-up Assessment[3]		X	X	X

[1] While inpatient, the results of SOC echocardiographic assessments if performed will be used for the study at the approximate time points of: 24 hrs, 3 days, 1 wk, wkly until sub-systemic or >6 wks old

[2] Head MRIs will be performed on all patients prior to discharge, and then as indicated.

[3] Neonatal Follow-up Assessment – Please refer to the neonatal follow-up assessment table below for administration detail

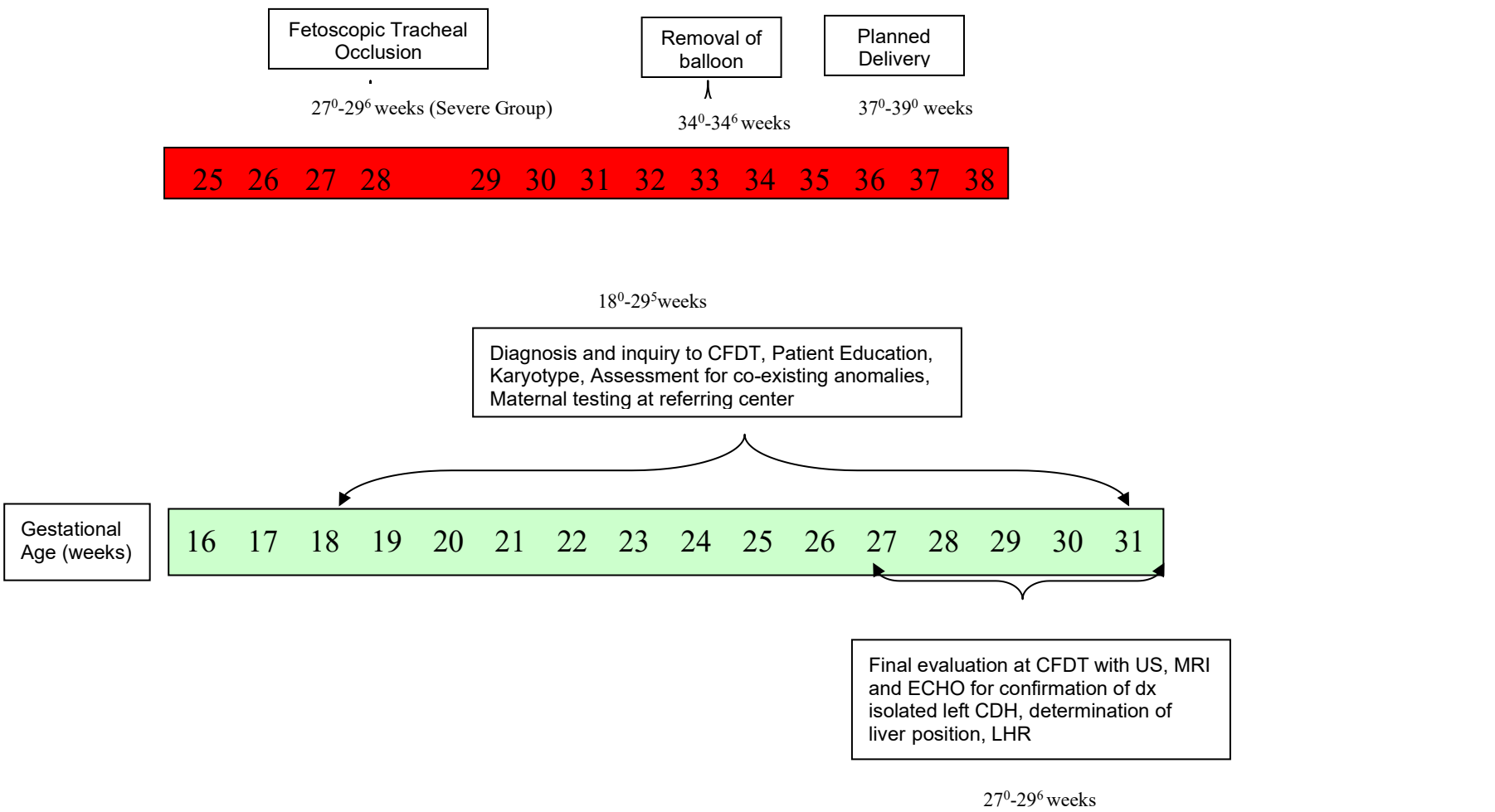
Table 3: Schedule of Neonatal and Parental Follow-up Assessments (Time points based on corrected age) **<u>Neonatal Follow-up:</u>**	**Test**	**6 month visit** (+/-1 month)	**12 month visit** (+/-1 month)	**24 month visit** (+/-1 month)
Language Receptive/Expressive**	Bayley Scales of Infant and Toddler Development, 4th Edition	X	X	X
Gross Motor**	Bayley Scales of Infant and Toddler Development, 4th Edition	X	X	X
Fine Motor**	Bayley Scales of Infant and Toddler Development, 4th Edition	X	X	X
Cognitive**	Bayley Scales of Infant and Toddler Development, 4th Edition	X	X	X
Behaviour	Brief Infant-Toddler Social and Emotional Assessment (BITSEA) Modified checklist for Autism in Toddlers (M-CHAT-R)			X X
Interim Medical History	Medical history, assessment of growth, physical exam, neurological exam, assessment of feeding issues	X	X	X
<u>Parental Follow-up:</u>				

Psychological Testing *	Beck Depression Inventory -II		X	X
Parent Assessments - to be completed by the mother and her partner	Parent Stress Index		X	X
	Impact on Family Scale		X	X

*Both parents to perform BDI-II if available. If a parent has missed a BDI-II assessment at a previous visit, BDI-II will not be performed at a subsequent visit

** Prior to January of 2021, the Bayley Scales of Infant and Toddler Development, 3rd Edition was used for Neonatal Follow Up.

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

Despite advances in prenatal diagnosis and postnatal therapies, including ECMO, inhaled nitric oxide therapy, and ventilator strategies that minimize ventilator-induced lung injury, morbidity and mortality rates for babies with severe CDH remain high. Between January 2006 and December 2010, we provided prenatal and postnatal care for 64 patients with isolated left CDH. Overall survival was 63% and use of extracorporeal membrane oxygenation (ECMO) was 33%. Observed/expected lung to head circumference ratio (O/E LHR) is a tool validated in 354 fetuses with unilateral isolated CDH evaluated between 18 and 38 weeks gestation.[1] For O/E LHR < 25%, survival was dismal at 1/9 or 11% (CHOP experience, not published). We have updated survival data for 2010-2015 showing 10/29 (34%) in the liver up O/E LHR <25% group and 11/24 (46%) in the liver up O/E LHR 25-<30% group. For the same time period amongst 5 of the centers in the NAFTNet FETO Consortium the survival for liver up O/E LHR < 25% was 18/45 (40%) and O/E LHR 25-<30 % 20/33 (61%). Please see revised table and bar graphs below.

LHR O/E LHR	Liver up		Liver down	
	Non Survivor	Survivor	Non-Survivor	Survivor
< 25%	27 (60%)	18 (40%)	0 (0%)	2 (100%)
25-<30%	13 (39%)	20 (61%)	2 (14.3%)	12 (85.7%)
30-<35%	10 (27%)	27 (73%)	2 (10.5%)	17 (89.5%)
35% and beyond	5 (11%)	42 (89%)	7 ((9.6%)	66 (90.4%)

In reviewing Jani et al> (2009), FETO was performed on 20 moderate cases of left CDH (LHR 26-30), and survival was reported at 70%. [45]

Since July 2004, we have also prospectively followed all survivors with CDH in an interdisciplinary follow up program, uncovering striking morbidities in neuromuscular tone and neurodevelopmental status. Median age at last assessment was 24 months (range, 6-62). Average, mixed, mildly delayed, and severely delayed scores for neurocognitive and language skills were found in 49%, 19%, 17% and 15%, respectively. Psychomotor scores were normal, mildly delayed, and severely delayed in 46%, 23%, and 31%, respectively. Autism was present in 7%. Abnormal muscle tonicity was found in 51% (49% hypotonic, 2% hypertonic). [2]

The rationale for fetal therapy in severe CDH is to restore adequate lung growth for neonatal survival. Prenatal tracheal occlusion (TO) obstructs the normal egress of lung fluid during pulmonary development leading to increased lung tissue stretch, increased cell proliferation,

and accelerated lung growth. Early studies of open TO were associated with survivals of 13 to 33% (expected survival 0%) and significant morbidities.[8,9] Subsequently, techniques for fetoscopic TO were developed and showed improved outcomes.[10,11] In November 2003, a NIH sponsored trial of fetoscopic TO showed no survival or morbidity advantage.[12] Increased survival/morbidity was not found in the 2003 study partly due to a lack of standardization with the procedure technique performed on a less severe group of patients (LHR $\leq$ 1.4). In experimental animal studies, several groups have shown that prolonged periods of TO diminish the number of alveolar epithelial type-II cells leading to decreased levels of pulmonary surfactant gene and protein expression.[13,14,15,16] Restoring the normal flow of lung liquid leads to recovery of type II cells and endogenous surfactant protein gene expression.[16,17,18] European colleagues have developed endoscopic equipment [4] and techniques to position and remove endoluminal tracheal balloons.[5,6,7] Recently, the Belgium group published summary results of FETO showing an improved survival in 175 patients with isolated left CDH from 24% to 49%.[7]

1.1 Introduction

Techniques and equipment for tracheal occlusion and release have advanced. Recent experience in Europe is promising. We propose a feasibility study prior to enrollment in a multi-institutional study for FETO. We have the commitment of Dr. Jan Deprest to assist us in training to perform the technique. This feasibility (pilot) study is a prerequisite for the institution's participation in the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) Trial for severe Pulmonary Hypoplasia, an international randomized controlled trial comparing FETO to expectant management in CDH.
[http://clinicaltrials.gov/ct2/show/NCT01240057?term=deprest+AND+hernia&rank=2]

1.2 Name and Description of Investigational Product or Intervention

Investigational devices used in this study include the BALT Goldbal 2 single use balloon and catheter system.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

Wilson et al and DiFiore et al demonstrated, in fetal lamb models of bilateral nephrectomy and CDH respectively, that TO could prevent pulmonary hypoplasia and accelerate lung growth.[19,20] In the study by DiFiore et al, diaphragmatic hernias were created in fetal sheep at 90 days' gestation (term = 145 days) and TO performed at 110 days' gestation. Parameters which showed improvement included increased lung volume: body weight ratio, alveolar surface area, and alveolar number. Total lung DNA and protein were increased when compared to CDH controls. In functional studies, the TO group showed improved compliance, higher PaO_2's and lower $PaCO_2$'s. Hedrick and colleagues confirmed accelerated lung growth in a fetal lamb CDH model and showed marked improvement in pulmonary function in CDH + TO animals compared to those with uncorrected CDH.[21]

Papadakis et al found that temporary TO followed by tracheal release allowed type II cell recovery, re-expression of surfactant proteins, and improved compliance in the sheep model.[22] Using normal fetal sheep, Flageole et al found preserved type II pneumocytes

following temporary tracheal ligation compared to normal and prolonged TO controls.[18] In another group of fetal sheep, diaphragmatic hernias were created at 90 days gestation, and TO performed from 108-122 days gestation. Lung growth was not induced but functional studies at term improved.[23] Luks et al found improved peripheral pulmonary arterial medial wall thickness following temporary TO in sheep CDH compared to CDH controls.[24] Reversal of TO before birth may give the lungs time to develop mature type II pneumocytes and prevent hydrops with its resultant preterm labor.

In prior studies, the sheep CDH model was used successfully to show improved functional, biochemical, and morphometric parameters following administration of prenatal glucocorticoids.[25,26] The sheep hypoplastic lung model was later used to trial a new ventilator.[27,28] This laboratory also has a history of successful use of the CDH sheep model.[29,30,31] In preliminary studies of fetal sheep, we have shown that our recent CDH model (CDH creation at 65 days gestation; term = 145 days) suffers from severe pulmonary hypoplasia with inability to maintain survival in any of six lambs beyond 40 minutes. Profound acidosis, hypoxia, and hypercapnia characterized the blood gases. The lung weight to body weight of the CDH animals was markedly lower in CDH animals compared to sham controls. TO at 110 days gestation restored lung mass (Figure 3A), but did not affect static compliance when compared to CDH controls (Figure 3B), due, in part, to a reduction in pulmonary surfactant protein synthesis.[16] Temporary TO in CDH animals restored pulmonary surfactant proteins expression, but failed to improve neonatal gas exchange and lung compliance.[16] Histologically, alveolar wall thickness remained elevated in CDH lambs that underwent either temporary or prolonged TO therapy. A single course of maternal steroids decreased alveolar wall thickness in CDH lambs following prolonged TO and, when combined with postnatal surfactant therapy, normalized lung compliance and gas exchange.[32] Prenatal steroid exposure reduced aberrant muscularization of pulmonary arterioles induced by CDH.[33]

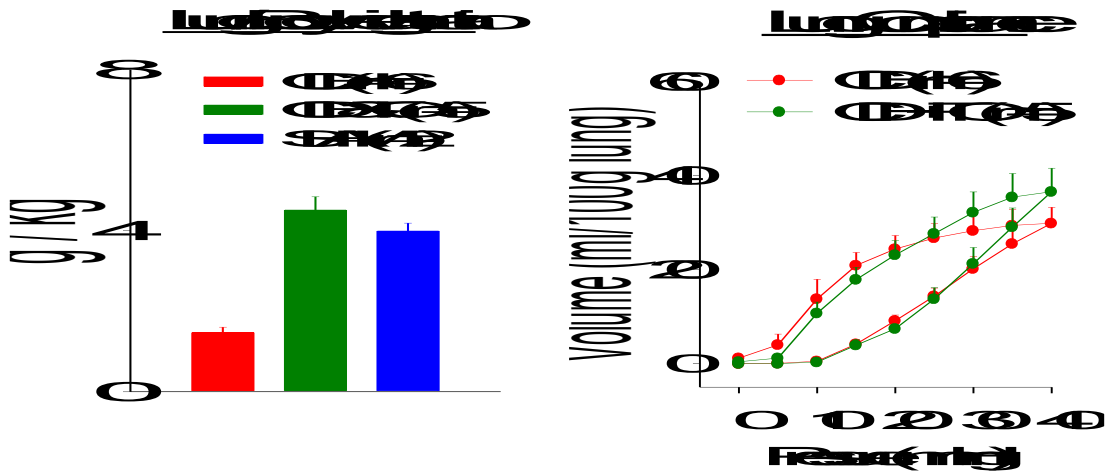


Fig 3. A) Lung weight to body weight was markedly lower in CDH animals (red) compared to controls (blue). B) TO restored lung mass (green), but did not affect static compliance.

1.3.2 Clinical Studies in Children

Refer to Section 1.5 Relevant Data & Literature

1.4 Selection of Drugs and Dosages

All patients will undergo FETO with standardized preoperative, intraoperative, post-operative care and delivery. All medications will be administered using standard of care procedures. Patients undergoing FETO surgery will sign a separate sedation consent form.

Maternal corticosteroids (betamethasone 12 mg intramuscularly and repeated once at 24 hours) will be administered 48 hours prior to fetoscopic balloon removal (due to risks of preterm delivery associated with instrumentation) or for impending preterm delivery. A second course (betamethasone12 mg IM 24 hours apart) may be given prior to balloon removal or delivery if the first course was given more than 14 days prior to gestational age 36 weeks 6 days.

See Appendix V for list of drugs utilized in study procedures.

1.5 Relevant Literature and Data

The natural history of CDH

CDH is a surgically correctable defect, but the essential problem is the resulting pulmonary hypoplasia, causing ventilatory insufficiency and pulmonary hypertension in the neonatal period. Prenatal referral, high caseload, and advanced neonatal care improve survival but the

condition is still lethal in around 20-30% of cases (Table 4).

Table 4: Recent series on postnatal outcome of isolated CDH. Some units report survival rates after transfer of the neonate (*), and do therefore not include the hidden mortality. TOP: Termination of pregnancy; n.a.: not available, **submitted for publication

Study	Number of cases	TOP rate	Survival Rate
Gallot 207	314	7%	63%
Stege 2003	185	n.a.	70%
*Sartoris, 2006	244	n.a.	70%
Hedrick, 2007	89	n.a.	66%
Datin-Doriere 2008	99	20%	63%
*Mettauer 2009	147	n.a.	77%
Grushaka 2009	121	n.a.	81%
Mt Sinai, Toronto 2011**	86	15%	65%

[34]

Prognosis in CDH is determined by fetal imaging techniques for fetal liver position and LHR.

Fetal surgery in fetuses with severe CDH: current experience

Fetal tracheal occlusion (TO) prevents egress of lung liquid, leading to stretch-induced growth of airways and vessels. The experimental background on effects of TO was recently summarized by Khan.[35] TO triggers lung growth, and in utero, reversal of the occlusion prompts pulmonary maturation.[18,36] Experimentally an endoscopic technique of tracheal occlusion using a balloon was developed.[36] In 2004, it was first applied clinically and referred to as Fetoscopic Endoluminal Tracheal Occlusion (FETO).[6] This clinical experience prompted the abandonment of other occlusion methods by European fetal treatment centers. The report from the FETO consortium (Leuven, Barcelona and London) provides outcome information following TO in 210 fetuses with severe pulmonary hypoplasia secondary to CDH [7]. FETO was performed at a median gestation of 27.1 (range 23.0-33.3) weeks. The median duration of FETO was 10 (range 3-93) minutes. Removal of the balloon was prenatal either by fetoscopy or ultrasound guided puncture, intrapartum by EXIT, or postnatal either by tracheoscopy or percutaneous puncture. Spontaneous preterm rupture of membranes prior to 32 weeks (PPROM) occurred in 47.1% of cases at a median of 30 days after FETO, with 16.7% occurring within 3 weeks of the procedure. This is a significant difference from what was reported in the earlier clinical experience with TO at San Francisco where PPROM occurred in 100% cases prior to 32 weeks gestation.[12] Operation time was a predictor of PPROM, and was dependent on the surgeon's experience. Delivery took place at a median of 35.3 weeks, with 30.9% of deliveries prior to 34 weeks, and 12.6% prior to 32 weeks. (Table 5).

Table 5: Occurrence of PPROM and early delivery (<32 wks) in 210 consecutive cases of FETO (GA at balloon insertion 23-33 wks). Data from the FETO consortium. [7]

Occurrence of PPROM (all cases)	47.1%
PPROM & delivery < 32 wks	9.3%
Preterm delivery < 32 wks, without PPROM	3.6%
Delivery < 32 wks	12.9%
PPROM prior to 32 weeks but delivery beyond 32 wks +	36.8%

[34]

In 204 cases, the babies were live born at 26.0-41.0 weeks GA, and 98 (48.0%) were discharged from the hospital alive. On the basis of the relation between survival and observed/expected LHR in expectantly managed fetuses with CDH, survival rates in fetuses with isolated left CDH treated with FETO increased from 24.1% to 49.1%.[7]

1.6 Compliance Statement

This study will be conducted in full accordance of all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to all pregnant women, fetuses, children or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the study is to determine the feasibility of performing FETO surgery and removal of the BALT balloon at CHOP. We hypothesize that FETO can be performed and may increase survival and decrease morbidity when compared to standard prenatal care for the treatment of severe CDH.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine whether the FETO intervention is feasible and safe to conduct in fetuses with severe left CDH (O/E LHR < 25%).

2.2 Secondary Objectives (or Aims)

Secondary objectives include:

- Demonstrate fetal lung growth due to successful FETO.
- Determine survival rate and outcome measures of FETO patients.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

FETO is an un-blinded non-randomized pilot study conducted in the CFDT at CHOP. Please refer to Figure 2 for a timeline referencing the study phases listed below.

3.1.1 Screening Phase

Potential subjects (pregnant women) will undergo a comprehensive fetal evaluations at the CFDT to confirm the diagnosis of CDH. Study eligibility will be based on the results of the clinical assessments (Table 1).

The potential subject will be screened using the protocol inclusion and exclusion criteria. Pregnant women, 18 and older meeting the eligibility criteria will be approached to discuss the FETO trial.

Informed Consent

Pregnant women, 18 and older meeting the eligibility criteria will be approached to discuss the FETO trial. Parental/guardian permission (informed consent) will be obtained prior to any study related procedures begin.

Once preoperative evaluation confirms that the patient is eligible for fetal intervention, the family will be offered enrollment. The voluntary nature of participation will be stressed throughout the discussions.

3.1.2 Study Treatment Phase (start of the study intervention)

Patients will undergo FETO with standardized CFDT preoperative, intraoperative, post-operative-care and delivery.

Study Treatment Phases includes the following:

- Balloon Insertion
- Monitoring Procedures
- Balloon Removal
- Delivery

3.1.3 Follow-up Phase

The follow-up phase will be conducted from birth to 24 months of age (corrected age). Follow-up will include bronchoscopy, brain imaging, audiology examinations, pulmonary function testing, chest radiographs, and developmental assessments. Please refer to tables 2 and 3 for follow-up visit details.

3.2 Allocation to Treatment Groups and Blinding

This is a pilot clinical trial for fetuses with US O/E LHR < 25%. Blinding will not occur. All pregnant women carrying a fetus with a prenatal diagnosis of CDH and referred to the CFDT at CHOP will be evaluated for eligibility.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per mother and child will be up to 877 days, with up to 82 days screening, up to 55 days in the intervention phase, and 744 days in delivery and follow-up.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at The Children's Hospital of Philadelphia.

Initial enrollment included 10 Subjects (IDE Approval: G140236). After 10 subjects were reached, an IDE Supplement Application was submitted to receive approval for an additional 5 subjects from the FDA. The FDA approved the request for 5 additional subjects on March 4, 2021.

An amendment was submitted for IRB review and approval before enrolling the additional 5 subjects beyond the 10 currently approved by the FDA.

15 subjects will be enrolled to produce 15 evaluable families. Recruitment will stop when approximately 15 subjects have been enrolled.

Subjects refer to mother, father/partner and child.

3.4 Study Population

3.4.1 Inclusion Criteria

1) Pregnant women age 18 years and older
2) Singleton pregnancy
3) Normal fetal karyotype with confirmation by culture results. Results by fluorescence in situ hybridization (FISH) will be acceptable if the patient is > 26 weeks or chromosomal microarray with non-pathologic variants
4) Fetal Diagnosis of Isolated Left CDH with liver up
5) Severe: Gestation age at enrollment prior to 29 weeks plus 5 days for US O/E LHR <25%
6) Family considered and declined option of termination of the pregnancy at less than 24^0 weeks
7) Family meets psychosocial criteria
8) Informed consent

3.4.2 Exclusion Criteria

1) Patient < 18 years of age

2) Multi-fetal pregnancy

3) Rubber latex allergy

4) Preterm labor, cervix shortened (<15 mm at enrollment or within 24 hours of FETO balloon insertion procedure) or uterine anomaly strongly predisposing to preterm labor, placenta previa

5) Psychosocial ineligibility, precluding consent:

    - Inability to reside within 30 minutes of CHOP and inability to comply with the travel for the follow-up requirements of the trial
    - Patient does not have a support person (e.g. spouse, partner, mother) available to stay with the patient for the duration of the pregnancy at CHOP

6) Right sided CDH or bilateral CDH, isolated left sided with O/E LHR ≥25% (measured at 18^0 to 29^5 weeks) as determined by ultrasound[1]

7) Additional fetal anomaly by ultrasound, MRI, or echocardiogram at the fetal treatment center. Exclude chromosomal abnormalities, associated anomalies recognized to alter survival prognosis (ie. CDH and congenital heart disease) or presence of an underlying genetic syndrome (ie. Fryns). No cases will be removed post hoc if abnormalities are discovered in the course of post-operative monitoring

8) Maternal contraindication to fetoscopic surgery or severe maternal medical condition in pregnancy

9) History of incompetent cervix with or without cerclage

10) Placental abnormalities (previa, abruption, accrete) known at time of enrollment

11) Maternal-fetal Rh isoimmunization, Kell sensitization or neonatal alloimmune thrombocytopenia affecting the current pregnancy

12) Maternal HIV, Hepatitis-B, Hepatitis-C status positive because of the increased risk of transmission to the fetus during maternal-fetal surgery. If the patient's HIV or Hepatitis status is unknown, the patient must be tested and found to have negative results before enrollment

13) Uterine anomaly such as large or multiple fibroids or mullerian duct abnormality

14) There is no safe or technically feasible fetoscopic approach to balloon placement

15) Participation in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial in a previous pregnancy

Pregnant women and fetuses that do not meet all of the enrollment criteria will not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening and Informed Consent Process

Visit 1 - <u>Screening</u>

Potential subjects will be identified by review of the patient's standard of care records from their comprehensive CFDT evaluation to determine eligibility:

- Comprehensive obstetrical ultrasound examination, including documentation of cervical length, gestational age, biometry, liver herniation, hepatic vasculature, sonographic lung volume, amniotic fluid level, membrane status, and LHR calculation
- Maternal MRI to confirm fetal liver herniation
- Fetal Echocardiogram to rule out structural abnormalities
- Demographics/Medical History
- Maternal history
- Physical Examination
- Vital Signs
- Height & Weight
- Laboratory tests including karyotyping
- Prior/concomitant medications
- Psychosocial evaluation to identify family support and possible confounding social issues
- Patient Education including: CDH description, prenatal and neonatal development, general expected outcomes and management options

<u>Informed Consent Process</u>

The Study-Sponsor/ Principal Investigator will review the informed consent with eligible patients. This will include a:

- Description of study rationale and design
- Review of Inclusion/Exclusion Criteria
- Focused interview by the PI or designee to afford potential pregnant women formal opportunity to examine what they have learned about the research study in the course of their evaluation and discuss how they feel about enrolling in the research study

No research procedures will be performed prior to obtaining voluntary informed consent.

Research Procedures

- Beck Depression Inventory II – This assessment will be completed by both parents. If a mother endorses clinically significant symptoms as assessed by the BDI-II score equal to or greater than 17 she will be referred to the CFDT Psychologist. The Psychologist will further evaluate the parent for additional risk factors, counsel, continue to follow the family, and offer mental health resources and crisis services when clinically indicated.
- Clearance for surgery by anesthesia and the obstetrical staff with standardized CFDT preoperative procedures.
- Transvaginal ultrasound – Performed to determine cervical length within 24 hours of FETO Balloon Insertion Procedure.

4.2 Intervention Phase

The study procedure phase includes FETO surgery, weekly and bi-weekly monitoring after surgery, and removal of the balloon. Below please find details regarding each visit included in this phase.

4.2.1 Visit 2 – FETO Surgery (All Procedures are Research Procedures)

- Clearance for surgery by anesthesia and the obstetrical staff using standardized CFDT preoperative clinical protocol for fetal surgery patients.
- FETO will be completed at 27 weeks 0 days – 29 weeks 6 days.

The procedure will be completed under ultrasound guidance along with maternal IV sedation, local anesthesia, and perioperative tocolysis using indomethacin. Fetal analgesia and immobilization will consist of fentanyl, atropine and vecuronium. See Appendix V for list of drugs utilized in study procedures. This list is not all inclusive.

- A 10 Fr pyramidal trocar, 1.3 mm fetoscope within a 3.0 mm sheath (Karl Storz, Tuttlingen, Germany), and a detachable balloon occlusion (BALTACCI-BDPE, Balt, Montmorency, France) system will be used.
- Tocolysis with indomethacin: a 50 mg loading dose given preoperatively and then 25 mg every 6 hours for 24 hours. Breakthrough contractions treated with IV Magnesium sulfate.
- A gastric acid reducer will be given prior to the procedure.
- Serial measurements of sonographic lung volume and LHR will begin 24-48 hours following surgery and continue weekly by targeted ultrasound evaluation.
- The expected hospital course is 23-48 hours; however, it is possible that the patient will be hospitalized for complications or preterm labor. The patient will then be discharged to a nearby accommodation. Subject will be required to reside within 30 minutes of CHOP in anticipation of delivery.

Patients will be on modified bed rest for the first 2 weeks post discharge, but subsequently allowed to graduate to moderate activity if the uterus is quiescent. Assess possible adverse events/ serious adverse events

Pre and post-operative care will follow usual clinical care management practice including but not limited to antibiotics, pain medication, antipyretics, medications to relax the uterus for fetal external version (if indicated), etc.

4.2.2 Visit 3 Weekly Check-ups (Balloon Insertion to Delivery, starting one week after procedure)

Weeks 28, 29, 30, 31, 32,33, 34, 35, 36, 37, 38, 39^0

Standard of Care Procedures:

- Standard of care procedures will occur as part of the prenatal follow up visit for CDH
- Biophysical profiles will be performed weekly beginning at 34 weeks.
- Targeted Maternal MRI and Fetal ECHO will be performed as clinically indicated.

Research Procedures (Only performed while the balloon is in place):

- Targeted ultrasonography for measurements of sonographic lung volume & LHR will begin within 24-48 hours following balloon insertion and continue weekly.
- Targeted ultrasonography for measurements of amniotic fluid level & membrane status
- Fetal Growth Surveillance will occur every four weeks after balloon insertion
- Assess possible adverse events/ serious adverse events

4.2.3 Visit 4 – Removal of Balloon (all procedures are research)

Fetoscopic removal of the balloon occlusion will be performed at 34 weeks 0 days to 34 weeks 6 days.

The maximum duration of balloon implantation, if placed at 27 weeks 0 days and removed in the 34^{th} week, is 7 weeks. For those balloons placed later in gestation or removed earlier electively or emergently, the duration will be shorter.

- Clearance for surgery by anesthesia and the obstetrical staff. Anesthesia regional (spinal or epidural) in preparation for possible emergent delivery.
- A dose of maternal corticosteroids will be administered at 48 and 24 hours prior to removal of balloon occlusion. A second course (betamethasone 12 mg IM 24 hours apart) may be given prior to balloon removal or delivery if the first course was given more than 14 days prior to gestational age 36 weeks 6 days.

- Breakthrough contractions will be treated with nifedipine.
- Procedure – attempted US guided percutaneous needle puncture through maternal abdomen using 20 gauge needle, if feasible. If needle aspiration unsuccessful, fetoscopic removal of balloon.
- Procedure – attempted initial fetoscopic removal as safest option under the following conditions (e.g., membrane status, location of placenta, or fetal positioning, etc.)
- If percutaneous needle puncture is not feasible, and fetoscopic removal of balloon is successful, the balloon and tracheal aspirate cells are to be packaged by OR staff and shipped by study staff to Massachusetts General Hospital under a Material Transfer Agreement.
- Assess possible adverse events/ serious adverse events

4.2.4 Visit 5 – Delivery

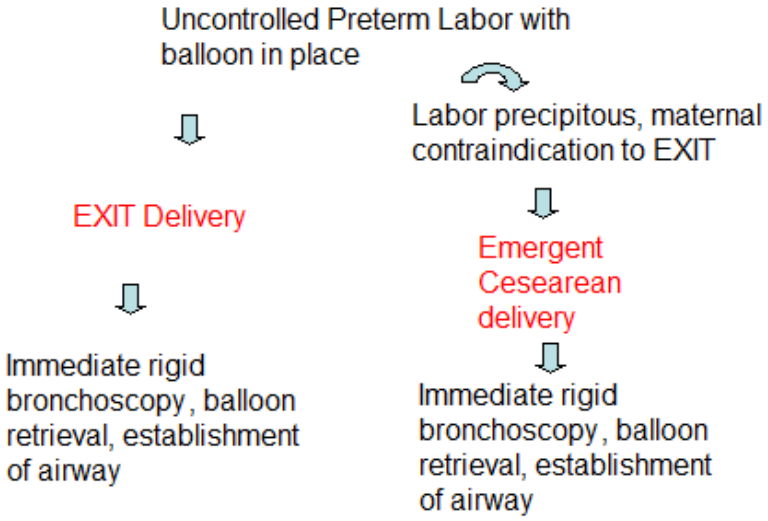
Planned delivery will occur after 37 weeks. Timing for induction of labor at 37 weeks 0 days to 39 weeks 0 days will depend upon favorable status of the cervix. Cesarean section will be based upon standard obstetrical indications.

Standard of Care Procedures:

- Surfactant will be administered if balloon is removed at delivery, delivery at less than 34 weeks, or if the baby is born less than 48 hours after FETO release.
- Delivery
- Standard postnatal care
- **Appendix IV:** CHOP CDH Delivery and NICU Guidelines

Research Procedures:

- For preterm labor before the balloon has been removed, pregnant woman will be admitted for tocolysis, maternal corticosteroids and attempt to maintain pregnancy.
- For preterm labor before balloon has been removed that cannot be controlled by tocolysis, delivery by Ex Utero Intrapartum Therapy (EXIT), if maternally safe, may be performed. Emergent EXIT algorithms used as standard practice for fetuses with obstructed airway from other causes initiated. Systems are already in place for mothers presenting in labor prior to planned EXIT delivery (Appendix III).
- For precipitous preterm labor or maternal indications when EXIT cannot be performed, delivery by cesarean section may be performed followed by immediate bronchoscopy and establishment of airway.
- In the event that a bronchoscopy is performed, the balloon and tracheal aspirate cells are to be packaged by OR staff and shipped by study staff to Massachusetts General Hospital under a Material Transfer Agreement, if feasible.



- BDI-II (within 1 month of delivery) – This assessment will be completed by both parents (if present).
- Assess possible adverse events/ serious adverse events

4.3 Follow-up Phase

The follow-up phase will be conducted from birth to 24 months of age. A resuscitation team from neonatology and pediatric surgery will be present at delivery. A standardized protocol will be utilized for postnatal care, using lung protection strategy.[34,38]

See Appendix IV, for Newborn/Infant Intensive Care Unit Optimal Care Guidelines.

- Use of ECMO
- Normalization of pulmonary vascular resistance. Utilization of pulmonary vasodilators (e.g. inhaled nitric oxide, sildenafil) will be standardized. Echocardiographic estimates of right ventricular end diastolic pressure will be performed within 24 hours, 3 days, 1 week, and then weekly until sub-systemic or > 6 weeks old. Echocardiographic assessments will also be performed at 6 months, 12 months and 24 months.
- Bronchoscopy prior to initial discharge to document presence or absence of tracheomalacia performed on all enrolled subjects **(research procedure).**
- Brain imaging. Head MRI will be performed on all patients prior to discharge, and then as indicated.
- Audiology examinations prior to discharge and then every 6 months.
- Pulmonary function testing (PFT) using Collins-Verraris Infant PFT Equipment at 6 months, 12 months, and 24 months.

- Chest radiograph prior to discharge and at 12 months and 24 months.
- Medical record review
- Developmental assessment: All parents and their infants will be required to return to the assigned treatment center for standard of care medical examinations and **research related neonatal developmental assessments** at 6 months, 12 months, and 24 months and research related parental assessments at 12 months and 24 months. Follow-up visits are based on corrected age.

Please refer to tables 2 and 3 for follow-up visit details.

4.3.1 Visit 6 – NICU/Inpatient Stay

Standard of Care Procedures: The results of SOC procedures, if performed, will be used for the research study.

Standard postnatal care:

- Echocardiographic Assessments (The results of SOC echocardiographic assessments, if performed, will be used for the study at the approximate time points of 24 hrs, 3 days, 1 week, weekly until sub-systemic or >6 weeks old)
- Brain Imaging – Head MRI's will be performed on all patients prior to discharge, and then as needed
- Audiology Examination
- Chest Radiograph (CXR)

Research Procedures:

- Rigid Bronchoscopy will be performed on all enrolled subjects prior to extubation.

4.3.2 Visit 7 – 6 Month Follow-up (+/- 1 Month): (Based on Corrected Age)

Standard of Care Procedures: The results of SOC procedures, if performed, will be used for the research study.

- Echocardiographic Assessment
- Audiology Examination
- PFT
- Interim Medical History and Physical Exam

Research Procedures:

- Neonatal Developmental Follow-up Assessment – (Language Receptive/Expressive, Gross Motor, Fine Motor, Cognitive– refer to Table 3 and section 5.2.1 for specific test information)

Visit 8 – 12 Month Follow-up (+/- 1 Month): (Based on Corrected Age)

Standard of Care Procedures: The results of SOC procedures, if performed, will be used for the study.

- Echocardiographic Assessment
- Audiology Examination
- PFT
- CXR
- Interim Medical History and Physical Exam

Research Procedures:

- Neonatal Developmental Follow-up Assessment – (Language Receptive/Expressive, Fine Motor, Gross Motor, Cognitive, Psychological– refer to Table 3 and section 5.2.1 for specific test information)
- Parent Assessments- (Beck Depression Inventory –II, Parent Stress Index, Impact on Family Scale)

Visit 9 – 24 Month Follow-up (+/- 1 Month): (Based on Corrected Age)

Standard of Care Procedures: The results of SOC procedures, if performed, will be used for the study.

- Echocardiographic Assessment
- Audiology Examination
- PFT
- CXR
- Interim Medical History and Physical Exam

Research Procedures:

- Neonatal Developmental Follow-up Assessment– (Language Receptive/Expressive, Gross Motor, Fine Motor, Cognitive, Behavior, Psychological, refer to Table 3 and section 5.2.1for specific test information)
- Parent Assessments - (Beck Depression Inventory –II, Parent Stress Index, Impact on Family Scale)

4.3.2 End of Study

The study will conclude at the 24 month visit (Visit 10).

4.4 Unscheduled Visits

Pregnant women who have a fetus with the trachea occluded and require emergency or unscheduled care will be treated by staff at CHOP. All visits will be recorded.

4.5 Concomitant Medication

All prior and concomitant maternal medications prior to the screening visit and through the end of the pregnancy will be recorded in the subject's medical chart as part of their prenatal clinical management for CDH. Medications commonly used preoperatively, postoperatively and to prevent labor are listed in Appendix V.

4.6 Subject Completion/Withdrawal

Pregnant women/fetuses may withdraw from the study prior to FETO surgery or after balloon retrieval without prejudice to their care. They may also be discontinued from the study at the discretion of the investigator for lack of adherence to the study schedule, visit schedule, AE's, or if the investigator feels it is in the pregnant woman/fetus/child's best interest. The investigator may also withdraw those who violate the study plan, or to protect the pregnant woman, fetus or child for reasons of safety or administrative reasons. It will be documented whether or not each pregnant woman/fetus/child completes the clinical study. If the investigator becomes aware of any serious, related adverse events after the participant completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.7.1 Early Termination Study Visit

Pregnant women requesting withdrawal from study after balloon placement, but prior to retrieval, will be advised of lethal prognosis for the neonate if the balloon is not removed prior to delivery. Such an action would be against medical advice and may warrant initiation of legal proceeding to protect the neonate. If a pregnant woman/fetus enrolls and wishes to withdraw prior to balloon insertion, no additional information will be collected. If a pregnant woman/fetus withdraws after balloon removal, the final study visit will collect information based on the pregnant woman's upcoming follow-up visit. Please refer to Table 1 and 2 for a timeline and breakdown of procedures.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Study Evaluations and Measurements

The results of SOC procedures, if performed, will be used for the research study**.**

5.1.1 Medical History and Physical Examination

Comprehensive medical history, obstetrical history, social history, and physical examination and medical record review will be performed at multiple times throughout the study.

5.1.2 Vital Signs

Vital signs including blood pressure, heart rate, and respiratory rate will be performed as part of pre-operative work-up and at multiple times throughout the study.

5.1.3 Laboratory Evaluations

- Karyotype (standard of care test) or microarray testing.
- CBC
- Type & screen

5.1.3.1 Other Evaluations, Measures

Prenatal Evaluations

- High Resolution Fetal Ultrasound
- Targeted Maternal MRI
- Transvaginal ultrasound
- Fetal Echocardiogram
- Sonographic lung volume & LHR –24-48 hours following balloon insertion and weekly monitoring while the balloon is in place
- Amniotic Fluid & membrane status – weekly monitoring while the balloon is in place
- Fetal Growth Surveillance will occur every four weeks after balloon insertion
- Biophysical profile will be performed weekly starting at 34 weeks

Postnatal Evaluations

- Criteria for ECMO cannulation
- Pulmonary Vasodilators
- Echocardiograms – Performed with particular attention to structural anomalies and right sided pressures.
- Chest Radiograph – Performed as part of daily clinical care.
- Audiology Evaluation – BAERS & OAE's will be completed prior to discharge and at 6 month intervals as outlined above.
- Brain Imaging – Head MRI performed as soon as clinically stable to travel to scanner.
- Bronchoscopy – Bronchoscopy will be performed on all enrolled subjects prior to extubation.

- Pulmonary Function Testing – Measurements include lung volumes by plethysmography, forced expiratory flow from raised volume and specific compliance of the respiratory system (sCrs) by single breath occlusion technique.
- Developmental Testing – Refer to diagnostic testing in section 5.2.1

5.2 Efficacy Evaluations

While efficacy is not a primary endpoint of this study, measures will be used to assess the success of the FETO procedure. These are outlined in Section 6.2

5.2.1 Diagnostic Tests, Scales, Measures, etc.

Follow-up Methods and Duration

All children will be followed in the Pulmonary Hypoplasia Program, an established multidisciplinary follow-up program at The Children's Hospital of Philadelphia. Follow-up will include cardiology, pulmonary, medical, developmental/psychological, audiology, nutrition, surgery, and social work evaluations at designated intervals. Orthopedics, ophthalmology, speech, feeding team, and gastroenterology will see children as needed. The study will terminate following 24 month follow-up visit.

Description of Neurodevelopmental Assessments

Child Assessments: (All Assessments are Research Procedures)
Bayley Scales of Infant and Toddler Development-IV (BSID) - has three subscales, cognitive, language and motor scales. The cognitive scale includes items that assess sensori-motor development, exploration and manipulation, object relatedness, concept formation, memory and other aspect of cognitive processing. The language scale is composed of receptive communication and expressive communication items. The receptive subtest includes items that assess preverbal behaviors, vocabulary development, morphological development and social referencing and verbal comprehension. The expressive subtest assesses preverbal communication, vocabulary development and attributes, and morpho-syntactic development. The motor scale includes two subscales - fine motor and gross motor.

Brief Infant-Toddler Social and Emotional Assessment (BITSEA) – is a 42 item parent report screening tool designed to identify social-emotional/behavioral problems and delays in competence in children 12- to 36 months.

Modified Checklist for Autism in Toddlers, Revised (M-CHAT-R) – is a 20 item parent report screening tool to assess risk for autism in children 16-30 months. The clinician administered follow-up questionnaire is designed to increase specificity of the measure, and is given when the results of the parent report questionnaire fall in the "medium" risk range.

Parent Assessments: (All Assessments are Research Procedures)

Beck Depression Inventory II (BDI-II) - If the results of the BDI-II indicate that either parent is depressed, he or she will be referred to a mental health professional. (Both parents to perform BDI-II if available. If a parent has missed a BDI-II assessment at a previous visit, BDI-II will not be performed at a subsequent visit.)

Parenting Stress Index Life Events Stress Scale - a parent self-report, 19-item questionnaire. It focuses intervention into high stress areas and predicts children's future psychosocial adjustment. There exists a substantial body of published research linking these scores to observed parent and child behaviors and to child's attachment style and social skills.

Impact on Family Scale - a 15-item parent-report scale designed to assess the impact of the child's illness on four dimensions of the family: Financial, General Impact, Social Relations, and Coping, in addition to a total score. An evaluation of how vulnerable the parent sees their child and how they discipline them will be performed. It is widely agreed that the socio-economic status of families with disabilities are negatively affected and that socio-economic status can impact the results of neurodevelopmental testing. Therefore, socio-economic status will be ascertained.

5.3 Safety Evaluation

Safety of all pregnant women and fetuses will be monitored by the following:

- Assessments of adverse events/ serious adverse events
- Vital signs
- Physical exams
- Laboratory data
- Fetal growth surveillance
- Sonographic lung volume and LHR
- BDI-II

6 STATISTICAL CONSIDERATIONS

Statistics will be descriptive. Initial enrollment included 10 Subjects (IDE Approval: G140236). After 10 subjects were reached, an IDE Supplement Application was submitted to receive approval for an additional 5 subjects from the FDA. This is a pilot study to determine the safety of performing FETO in our institution. A total of 25 pregnant women/fetuses are approved for enrollment.

6.1 Primary Endpoint

The primary endpoint is the feasibility and safety of performing FETO as measured by the following:

- Recruitment of patients with severe CDH (LHR O/E < 25%)
- Successful placement and removal of balloon
- FETO placement and release operative times
- Non-emergent and emergent completion of FETO release
- Maternal complications (preterm labor, premature rupture of membranes, oligohydramnios, polyhydramnios, chorioamnionitis)
- Gestational age at delivery

Please note, there is no defined cutoff to determine success. With the approval of the G140236- IDE Supplement Application, approximately 25 cases will be completed prior to determining feasibility and safety. However, study enrollment would pause if stopping rules are met (as outlined in Section 8.2 Stopping rules section) and enrollment will proceed pending review/approval by appropriate safety and regulatory committees.

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- Fetal lung growth will be measured by the following:
    - lung volume and LHR measurements
- Outcome measures:
    - Survival at discharge from the hospital or at 6 months if still hospitalized
    - Grading of oxygen dependency (none, mild, moderate, severe as defined by Bancalari 2001)
    - Occurrence of severe pulmonary hypertension based on echocardiogram
    - Use of ECMO support
    - Number of days in neonatal intensive care unit
    - Number of days of ventilator support
    - Presence of periventricular leucomalaica at < 2 months postnatally
    - Presence of neonatal sepsis, intraventricular hemorrhage (grade 0-III), retinopathy of prematurity (grade III or higher)
    - Presence of gastro-esophageal reflux
    - Use of patch or muscle flap
    - Pulmonary function and volume testing at discharge and at one year of age

    - Neurodevelopmental testing at 6 months, 12 months, and 24 months
    - Day of surgery
- Route of delivery
- Total days maternal hospitalization

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries obtained at Visit 1.

6.3.2 Efficacy or FeasibilityAnalysis

The primary efficacy endpoint will be completion of FETO and FETO release. Secondary end points will include the information listed in section 6.2.

6.3.3 Safety Analysis

All pregnant women/fetuses entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study procedures will be summarized. SAEs (if any) will be described in detail.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.4 Sample Size

With the approval of the G140236- IDE Supplement Application, a sample size of 25 pregnant women/fetuses are approved for enrollment.

6.5 Interim Analysis

Interim efficacy and safety analyses will be conducted throughout the study. The Fetal Oversight Committee will act as the Data Safety Monitoring Committee (DSMC) for the CHOP FETO Trial.

See section 8.1 for specific DSMC responsibilities.

Section 8.2 for Trial Stopping Rules

7 INTERVENTION

7.1 FETO Description

The FETO procedure will include the use of the detachable balloon and catheter system (Balt, Montmorency, France) and devices provided by Karl Storz, Tuttlingen, Germany for the insertion and removal of the balloon and catheter system

Insertion of Balloon

FETO will be conducted at 27 weeks 0 days – 29 weeks 6 days gestation. The procedure will be performed under IV sedation with local anesthesia (lidocaine 1 or 2%) or combined spinal-epidural anesthesia (bupivacaine into the spinal space at the L3-L4 or L4-L5). General anesthesia should be avoided but is not excluded. In case of loco-regional or general anesthesia, mothers should be pre-hydrated with lactated Ringer's solution (1000 mL) and receive perioperative tocolysis (first line indomethacin, for breakthrough IV magnesium sulfate), antibiotics (cefazolin 2 g I.V. 8 hour; in case of allergy erythromycin or clindamycin) and gastric acid reductors. Nitroglycerin or terbutaline may be used to relax the uterus for fetal external version if indicated. The fetus will receive an IM injection of fentanyl 20 mcg/kg, atropine 20 mcg/kg and vecuronium 0.2 mg/kg. A second dose may be given if needed to immobilize the fetus.

A thin-walled flexible Teflon cannula (3.3 mm; Performa, Cook, Strombeek Beve, Belgium), loaded with a pyramidal trocar (11650TG, Karl Storz, Tuttlingen, Germany) is inserted into the amniotic cavity towards the fetal mouth. *In utero* access will be under ultrasound guidance by the Seldinger entry or direct trocar entry. The Seldinger entry is performed by inserting a 14-gauge spinal needle into the amniotic cavity. The stylet is removed and a guide wire is inserted through the needle into the amniotic sac. The needle is then removed and a 10 Fr cannula with blunt tipped dilating trocar is introduced over the wire into the amniotic sac. The trocar and wire are then removed. With direct entry the cannula is loaded with a pyramidal trocar and inserted into the amniotic cavity. The trocar is withdrawn and fetoscopic instruments inserted. Instruments include a slightly curved 10 Fr sheath loaded with a 1.3 mm fibre-endoscope (Karl Storz). The sheath allows insertion of the balloon occlusion system, consisting of a catheter loaded with a detachable latex balloon. It further has a side connector for amnio-infusion with Hartmann's solution heated to body temperature, for improving visualization and assisting in dilation of the vocal cords on entry of the trachea.

The endoscope should be introduced into the fetal mouth, following the tongue and palate, uvula, epiglottis and vocal cords as landmarks. Once inside the trachea, the carina should be identified to position and deliver the balloon between the carina and vocal cords. The balloon should then be inflated with 0.6 mL isotonic fluid (Goldball 2; Balt, Paris, France). The dimensions of the balloon in the inflated state are 7 mm in diameter by 20 mm in length.

The amniotic fluid should be restored to normal and intrauterine antibiotics given at the end of the operation.

The maximum duration of balloon implantation, if placed at 27 weeks 0 days and removed in the 34th week, is 7 weeks.ma For those balloons placed later in gestation or removed earlier electively or emergently, the duration will be shorter.

Patients will be given IV magnesium sulfate for breakthrough labor, in addition to indomethacin. Serial measurements of sonographic lung volume and LHR will begin 24-48 hours following surgery and continue weekly by targeted ultrasound evaluation. The expected hospital course is 23-48 hours; however, it is possible that the patient will be

hospitalized if complications or preterm labor occur. The patient will then be discharged to a nearby accommodation. Patients will be on modified bed rest for the first 2 weeks post discharge, but subsequently allowed to graduate to moderate activity if the uterus is quiescent.

Removal of Balloon

Balloon retrieval should be planned between 34 weeks 0 days and 34 weeks 6 days at the discretion of the CFDT. Mothers will receive betamethasone 12 mg IM on the 2 days prior to removal of the balloon.

The following algorithm is used for balloon retrieval according to the circumstances at the time of retrieval:

1. Attempted US guided percutaneous needle puncture through maternal abdomen using 20 gauge needle or fetoscopic removal of balloon at the clinician's discretion.

2. For precipitous preterm labor before the balloon has been removed, delivery by EXIT (if maternally safe) or cesarean section will be performed. If retrieval of balloon is unsuccessful prior to delivery, immediate bronchoscopy and establishment of airway will be performed.

Failed Procedure and Balloon Dislodgement:

If the fetus is not in the correct position to perform surgery, the fetus may be repositioned preoperatively or surgery will be rescheduled within the insertion timeframe (27 weeks 0 days-29 weeks 6 days). This is not considered an attempt, as patient will not receive sedation or anesthesia.

In addition, the balloon can dislodge spontaneously either by deflation or increasing tracheal diameter. Reinsertion of a balloon will be considered if this complication occurs within the FETO insertion timeframe (27 weeks 0 days). All procedures will take place at least one day apart.

In the TOTAL European trial, failure to access the fetal trachea was thus far less than 4%. This was solved by a second attempt.

Subject Relocation

It is standard of care to have all patients delivering in the SDU relocate near Philadelphia in anticipation of delivery. Gestational age at relocation varies by diagnosis and obstetrical indications. However, for this study, it is part of research for the pregnant woman to relocate near CHOP from 29 to 34 weeks gestation and while the balloon is in place. Since the fetus has an occluded airway it is imperative that the pregnant woman be within 30 minutes of the hospital at all times in the event of precipitous labor. All cases of neonatal death from balloon occlusion in prior European series occurred as a result of difficulty in removing the tracheal balloon outside of a FETO center where experienced personnel were not available

for delivery. [5] Conversely, no incidences of neonatal death occurred from balloon occlusion when the procedure and delivery were performed at a FETO center. Pregnant women are expected to have a support person with them and are instructed to travel by car or taxi directly to CHOP in the event of onset of labor.

Planned Delivery

Timing for induction of labor at 37 weeks 0 days to 39 weeks 0 days will depend upon favorable status of the cervix. Cesarean section will be based upon standard obstetrical indications.

Management of Maternal Complications

Management of Preterm Labor and Preterm Rupture of Membranes (PROM):

Obstetrical/Maternal care: Postoperatively, the patients will be monitored for uterine contractions, vaginal loss of amniotic fluid and fetal heart rate. The need for hospitalization and subsequent management will be determined by the managing fetal medicine specialist.

The patient will be treated for preterm labor or PROM as an inpatient in the labor and delivery unit. She will be at bedrest with bathroom privileges and have intravenous access maintained for administration of medications.

If preterm labor persists or significant cervical change occurs before the balloon has been removed, ultrasound guided percutaneous puncture of the balloon may be attempted. If percutaneous puncture of the balloon is unsuccessful, immediate bronchoscopy for balloon removal and establishment of airway will be performed as part of the EXIT procedure or at emergent cesarean delivery.

Use of Antenatal Steroids

Steroids will be used at the time of balloon removal or in the case of threatened preterm delivery through 36 weeks 6 days.

Management of Oligohydramnios

If the AFI is less than 5cm, the patient should be admitted and the fetal heart rate or non-stress test (NST) assessed every shift.

Management of Polyhydramnios

Polyhydramnios (AFI > 25) will be monitored at weekly visits and managed per standard of care. Approximately 40% of patients experience polyhydramnios. If patient is symptomatic an amnioreduction may be considered. The need for amnioreduction is rare, the exact percentage is not known.

Management of Intrauterine Growth Restriction
Intrauterine growth restriction (IUGR) is defined as estimated fetal size and weight less than the 10th percentile by ultrasound biometry. IUGR is managed per usual standard of care (fetal surveillance, amniotic fluid assessment and umbilical artery Doppler velocimetry).

Management of Fetal Distress
Recurrent late, prolonged or severe variable fetal heart rate decelerations, or a sinusoidal pattern, or prolonged bradycardia will be sufficient grounds for delivery if conservative measures such as maternal position change, administration of oxygen, and intravenous fluids are unsuccessful.

Membrane Separation
When local membrane separation is seen by ultrasound, patients will be placed on modified bed rest with bathroom privileges only. If the membrane separation progresses to a global membrane separation or extends to the placental cord insertion site, patients should be admitted to the antepartum service on bed rest, and a fetal monitoring performed every shift.

Please refer to:

- Appendix I: Description of the investigational devices and relevant devices for the FETO Procedure
- Appendix V: Medications Used During FETO Procedure
- Appendix VI: FETO Standard Operating Procedures for details on the balloon insertion and removal procedures.

7.1.1 Study Devices

Please refer to Appendix I for a list of investigational devices and relevant devices for the FETO Procedure.

7.1.2 Labeling

Please refer to **Appendix II** for a copy of the investigational device product labels.

All investigational devices listed in **Appendix 1** will be labeled in accordance with 21 CFR 812.5 "*CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."*

7.1.3 Treatment Compliance and Adherence

Postoperative ultrasound examination for fetal well-being, balloon position, and lung size will be done within a few days after the procedure, and then weekly.

Follow-up measures will include: balloon position, measurement of lung response (LHR), amniotic fluid volume (deepest pool), occurrence of membrane separation, and cervical length. Mothers will complete a physical examination at each visit.

Monthly comprehensive ultrasound examinations for fetal growth will be performed.

7.1.4 Device Accountability

Investigational devices (see Appendix I) will be maintained in the Fetal Operating Room in a locked cabinet that will only be accessible to designated study staff. Investigational devices will be shipped from BALT to CHOP where the devices will be labeled as investigational devices (see section 7.1.2). Records of study device shipment, receipt, use (device serial number and patient ID) and disposition will be maintained by the FETO study staff member using the FETO device accountability and receipt log. The purpose of this log is to ensure that the investigational device(s) will not be used for any person other than a study subject under the terms and conditions set forth in this protocol. The study device(s) is to be used by the investigator or designee and may not be used for any purpose other than that described in this protocol. At study completion, all device supplies will be used by the sponsor-investigator for the multicenter randomized trial.

8 SAFETY MANAGEMENT

This trial will be conducted under an investigator initiated IDE held by Dr. Holly L. Hedrick (Sponsor-Investigator). The Sponsor-Investigator will be responsible for the conduct of the trial and adherence to FDA Regulations 21 CFR 812.

The Sponsor-Investigator is also responsible for ensuring all study team members are appropriately trained and that the FETO study is conducted in accordance to the IRB approved protocol and IDE investigational plan. The Sponsor-Investigator will ensure that the IRB, DSMC, and FDA are appropriately informed regarding any safety implications or new manufacturing updates that occur during the course of the study investigation.

8.1 Reporting to the Data Safety Monitoring Committee

The Fetal Oversight Committee which will act as the Data Safety Monitoring Committee (DSMC) for the FETO Trial. The DSMC will be consulted at any time safety concerns arise during the conduct of the research study. The DSMC will convene after the first 3 patients enrolled have delivered and babies have been discharged from the hospital or at one year, whichever is sooner, to review study results.

The DSMC will review all AEs as stated in Section 8.4.1 and other interim safety data and will provide a report to the Sponsor-Investigator and the IRB.

Besides discontinuing recruitment until DSMC review in the case of a maternal death, if the number or imbalance of adverse events including fetal/neonatal deaths exceeds specified limits, recruitment will be discontinued until the DSMC has had a chance to confer.

Additionally the DSMC will review at least annually the following information:

- Summary of all AEs and SAEs by subject

- Protocol Deviations
- New information about the safety of the investigational device
- Updates to the safety profile of the device
- External SAEs that are both unexpected and related to the study intervention (if applicable)
- Protocol Amendments

Meeting minutes will be maintained and circulated for each DSMC meeting and will include the decision to proceed or stop the trial. The findings of this committee will provide binding recommendations to the sponsor-investigators and will be reported to the IRB at the time of continuing review unless the DSMC determines the study should be placed on hold.

If patient recruitment is low, the DSMC will be empowered to recommend modification of the sample size, the study design, or terminate the study for inadequate accrual or data quality.

8.2 Stopping Rules

Study Subject Stopping Rules: FETO insertion will be attempted up to three times in a single pregnant woman/fetus. If the procedure is unsuccessful after three attempts, the pregnant woman/fetus will not receive any additional fetal surgical procedures. Pregnant women/fetuses with successful and unsuccessful FETO insertion will be included in the study results as evaluable subjects. The procedure will be considered a failure if three unsuccessful FETO insertion attempts occur.

A single failed procedure (up to three attempts) is not considered failure in regards to the feasibility endpoint.

Trial Stopping Rules: The trial will be voluntarily placed on hold for the following reasons until the Sponsor-Investigator and the DSMC evaluate the safety of the trial and address any required changes to the investigational plan to decrease risk and improve safety:

- Maternal safety, although it is extremely unlikely, in the case of a single maternal death or significant medical or surgical complication, recruitment will be suspended until the oversight committee has reviewed the case.
- Fetal/neonatal safety, the perinatal period is the time of greatest risk of death for fetuses undergoing the experimental treatment.
- After 5 failed procedures, a failed procedure rate of 50% (10 Subjects) would result in a suspension of the study pending review by the oversight committee.

8.3 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

8.3.1 Eliciting Adverse Event Information

Adverse events will be captured through medical record review, self-report, physician evaluation, non-directive questioning during study visits, and/or clinical or research tests.

See Section 9.3.2 for a list of potential maternal and fetal complications as a result of the FETO intervention.

8.3.2 Recording Adverse Events

The Sponsor-Investigator will promptly review all adverse events and abnormal test findings to determine the causality to the investigational product. Expectedness of the adverse event will be based on the Sponsor-Investigator's determination and study documents (i.e. study protocol, informed consent, or IDE Application). All AEs (serious and non-serious) will be noted in the study records and recorded on the Adverse Event case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity/grade, duration, causality, relationship to the investigational product, and outcome of the event. Once an adverse event is detected, it will be followed to the extent possible until its resolution or until it is judged to be permanent. Any increase in severity of an adverse event will be captured as a new event.

SAEs will be documented as specified above and the relationship of each SAE to the study intervention will be characterized as outlined in section 8.6.1. The SAEs and UADEs will be closely followed and any changes in severity (improving or deteriorating) will be documented until resolved.

8.4 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.4.1 Adverse Event Reporting Period

Detailed information concerning adverse events (AEs) will be collected and evaluated throughout the trial. An AE is any event that is serious, deemed related to the study and/or unexpected in nature, severity, or frequency, or fits IRB definition of adverse event. Reporting of these events will be as follows:

- For any maternal, fetal or neonatal deaths or other life-threatening events associated with the FETO procedure:
    - A Serious Adverse Event Report will be sent by fax within 24 hours to the DSMC and IRB. In the case of a maternal death, recruitment will be discontinued until the DSMC has reviewed the data.
    - If an autopsy is performed, a copy of the report should be obtained and sent to the DSMC.
- All other events that are serious and/or unexpected in nature, severity, or frequency:
    - Promptly complete an Adverse Event Report

Besides maternal, fetal and neonatal deaths, the following are examples of adverse events to be reported.

- **Maternal events:** Stroke, drug allergy, uterine rupture, pulmonary embolus, ascites, spinal headache from epidural placement, amniotic fluid embolism, hemorrhage that requires blood transfusion or laparotomy, chorioamnionitis, pulmonary edema requiring diuretics or intubation, complications of general anesthesia, magnesium toxicity, chorioamniotic separation, bleeding from the placenta as a result of FETO placement or retrieval, anhydramnios or polyhydramnios.
- **Fetal /Neonatal Death:** As a result of the FETO procedure or failure to obtain an airway secondary to airway occlusion.

8.5 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a pregnant woman and/or /fetus who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or intervention, whether or not considered related to the medicinal product or intervention.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

8.6 Definition of Unanticipated Adverse Device Effect (UADE)

An UADE is 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 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)).

8.7 Definition of a Serious Adverse Event (SAE)

A SAE is any adverse drug or intervention experience that results in any of the following outcomes:

- Death as a result of the FETO Procedure
- A life-threatening event (at risk of death at the time of the event),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability/incapacity, or

- A congenital anomaly/birth defect in the offspring of a pregnant woman.

Important medical events that may result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the pregnant woman/fetus and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

8.7.1 Relationship of SAE to study device or other intervention

The relationship of each SAE to the study intervention will be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.8 IRB/IEC Notification of SAEs and Other Unanticipated Problems

This study population is focused on a subset of fetuses that are severely affected with CDH. There are multiple potential complications that may occur to the pregnant woman and fetus by nature of the diagnosis of CDH and interventions associated with the study. These would be expected and would not require reporting to the IRB except at continuing review unless they occur at a greater than anticipated frequency.

See Section 9.3.2 for a list of potential maternal and fetal complications to the FETO intervention.

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to pregnant women/fetus/children or others will also be reported promptly.

Written reports will be filed using the eIRB system and in accordance with the timeline below.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days

All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.8.1 Follow-up report

If a SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable.

8.9 Sponsor -Investigator Reporting to the FDA

The sponsor-investigator will report any intrauterine deaths or neonatal/infant deaths that are not identified as unanticipated adverse events within 30 days of becoming aware of the death. The Sponsor-Investigator will adhere to FDA Reporting Requirements 21 CFR812. Please see Appendix VII for all reporting requirements.

8.10 Medical Emergencies

If labor ensues prior to removal of balloon, attempted percutaneous puncture of balloon (success rate 10% in Dr. Deprest series, personal communication) will be performed and delivery may be vaginal. If balloon remains in place, EXIT procedure or cesarean section delivery will be followed by immediate bronchoscopy and establishment of airway. Surfactant will be administered for those fetuses delivered with no release, if delivery occurs at less than 34 weeks, or if the baby is born less than 48 hours after FETO release. Maternal corticosteroids (betamethasone 12 mg intramuscularly and repeated once at 24 hours) will be administered 48 hours prior to fetoscopic balloon removal (due to risks of preterm delivery associated with instrumentation) or for impending preterm delivery.

9 STUDY ADMINISTRATION

9.1 Data Collection and Management

A pregnant woman and her fetus/child will share the same subject ID number designated as (**A)** for mother and (**B)** for the fetus/child.

Study Consent forms will be stored in study binders. All binders will be stored in a locked cabinet within the research office of either the Division of General Surgery or The Clinical Research Support Office

Source documentation for study data will be the subjects medical records (paper and electronic).

Data from the following evaluations will be recorded on proprietary forms and stored in study binders: Bayley Scales of Infant and Toddler Development, Child Behavior Checklist, Beck Depression Inventory II, Parent Stress Index, and Impact on Family Scale.

Data will be managed and stored using the research-focused electronic data capture system REDCap. Information collected for this study includes data abstracted from medical records, procedures, interviews, and tests that are part of this research.

Data/CRFs will be stored in OnCore Clinical Trials Management System, a CHOP Research IS secured electronic data capture system.

Confidentiality & Security: A master list will be maintained containing the link between PHI and subject ID. This list will be kept in an electronic password protected file. Only study staff will have access to this file.

Anonymization & Destruction: Any data used will be coded by using a subject ID instead of a pregnant woman/fetus/child's name. The identifiers and study data will be retained in accordance with FDA guidelines.

9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy, and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. In order to protect patient's health information, only study staff will have the ability to access any information entered into the REDCap database. Each pregnant woman/fetus/child will be coded with a unique study number (Study ID A for the mother and Study ID B for the fetus/child). Scientific publications resulting from this study will not identify any patient by name. Only study staff will have access to the list linking the study code to specific patients taking part in the study. The list will be kept in a double password protected file, located in a research network supported by the Division of General Surgery, separate from clinic charts. All identifiable information will be used only for the needs of this study and to evaluate the results. Biospecimens transferred to Massachusetts General Hospital will be used for research purposes only and will remain deidentified. Biospecimens will be transferred with only a unique study code.

OnCore Clinical Trials Management System is a secure electronic data capture system with access controls and a data backup plan. The system is password protected. Only study team members will have access to subject data and case report forms stored in OnCore. Access to the system is monitored and logged for review if needed.

No identifiable data will be used for future studies without first obtaining IRB approval. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes).

9.3 Regulatory and Ethical Considerations

9.3.1 Data and Safety Monitoring Plan

This single center trial will be monitored internally by the CHOP Office of Research Compliance and Regulatory Affairs (OCRA). Below please find a detailed quality assurance and monitoring plan.

Quality Assurance Pre-Study Visit: A pre-study visit will be conducted after FDA IDE CHOP IRB approval prior to study start. This visit will be conducted by an OCRA staff member and the Program Manager of the IDE/IND Support Program to ensure the Sponsor-Investigator and study investigators have all required regulatory approvals, research training, and documents ready to conduct the trial.

Description of Monitoring Approaches: The Office of Research Compliance and Regulatory Affairs will begin monitoring activities for this study **after first subject** is enrolled into the study. Thereafter, ORCRA will monitor this study annually unless circumstances necessitate more frequent monitoring.

Monitoring activities will be guided by ICH E6 section 5.18.

- Source data verification for the first study subject enrolled:
  - 100% verification of eligibility criteria
  - 100% verification of all data points for set number of pregnant women/fetuses/children based on study accrual and enrollment
  - 100% review of select data points for remaining pregnant women/fetuses/children
  - 100% review of source documentation for safety events
  - 100% informed consent review
  - Review of on-going device accountability

Monitoring of subject data will be initiated at 100% verification of the data recorded. This may be amended, and a tapered approach to monitoring may be employed, if conduct and documentation of the study reaches a level of reliability that would permit valid conclusions based upon a sampling of data.

Annual Monitoring Visits: Monitoring visits will be scheduled annually or as directed by the CHOP IRB. The monitoring visit will include source data verification based on a percent of subjects enrolled to date.

Communication of Monitoring Reports: Monitoring reports (Appendix IX) will be communicated to the sponsor-investigator, the IND/IDE Support Program, DSMC and the CHOP IRB within 7 days after the monitoring visit has concluded.

Management of Noncompliance: Any serious or persistent noncompliant activity or violation that is observed during the course of monitoring will be reported to the sponsor-investigator. The OCRA Director will evaluate the report of noncompliant activities and a corrective action plan may be developed in conjunction with the IRB, the DSMC and

Research Administration in cases of serious or continued non-compliance as deemed necessary.

- **At the discretion of the CHOP IRB, OCRA may audit sponsor-investigator research more frequently in cases of serious or continued non-compliance.**

Examples of serious non-compliance may include lack of informed consent, enrollment of ineligible pregnant women/fetuses and significant treatment deviations. Other findings that increase risk to human subjects or institutional risk may also be considered serious. Continued or repeated non-compliance can increase risk to human subjects. Examples may include repeated significant deviations from study protocol.

Study Close-Out Visit: The Sponsor-Investigator will notify OCRA as soon as the last study subject is enrolled. A study close out visit will be performed by OCRA after all pregnant women and children have completed the study.

The visit will include the following:

- Final data reconciliation and assure all corrective actions from prior monitoring visit(s) have been implemented
- Review of all aspects listed in the End of Study Checklist Work Sheet. **See Appendix X.**

9.3.2 Risk Assessment

At CHOP, for the time period January 2006 through December 2010, neonates with prenatally diagnosed severe CDH and O/E less than 25% had mortality rate of 89% (8/9).

This is a severely affected population and the risks of postnatal neonatal death due to the diagnosis and unrelated to FETO are high.

Our background (experimental and clinical) work has identified a subset of severely affected fetuses with CDH who may benefit from prenatal intervention, allowing exclusion of patients who are mildly affected and therefore no intervention is warranted.

Maternal Risks

Potential complications as a result of FETO include:

- Amniotic fluid leakage into the maternal abdomen, leading to peritoneal irritation. This does not require any therapeutic intervention.
- PPROM is rupture of the amnion. In the absence of signs of infection, the patients will be managed expectantly with hospitalization, antibiotics, and possible tocolysis. If there is evidence of infection, then delivery will be expedited.
- Bleeding (in the absence of placental abruption) can occur from the uterine entry site leading to hemoperitoneum. This is usually self-limited but the patient needs to be monitored closely and, if necessary, treated with a blood transfusion. Prevention consists of ultrasound-guided insertion using color Doppler to avoid the placenta and vessels in the uterine wall.

- Local wound infection at the trocar site occurs in less than 1% of cases and is managed by the administration of antibiotics and/or local drainage. Polyhydramnios is excess amniotic fluid in the uterus. This could lead to discomfort for the mother and may require more frequent monitoring and possibly an amnioreduction.
- Loco-regional analgesia can be complicated by postdural puncture headache, failed sensory blockage, infection, hematoma, neurologic injury, and drug side-effects (pruritus, nausea and vomiting, urinary retention, hypoventilation, seizure, hypotension). The incidence of these complications is very low and no different than for other conditions where loco-regional is offered.
- Possible side-effects of the drugs commonly used after fetal surgery include:
  a. Magnesium sulfate - flushing, sweating, muscle weakness, nausea and vomiting, lethargy, blurred vision, excess fluid in the lungs necessitating supplemental oxygen;
  b. indomethacin - intestinal cramping, decreased amniotic fluid production, and constriction of the fetal ductus arteriosus; c. nifedipine – hypotension.
- Preterm labor can be induced by the intervention or by PPROM. Prophylactic tocolysis (first line indomethacin, Magnesium sulfate or nifedipine for breakthrough) will be given at the time of FETO. For balloon retrieval, first line tocolysis will be nifedipine, and Magnesium sulfate will be used for breakthrough. The risk for patients going into labor without PPROM or infection is less than 2%. If multiple balloon insertion attempts are needed, there may be an increased risk of preterm labor.
- Chorioamnionitis is inflammation of the fetal membranes (amnion and chorion) due to a bacterial infection. Any invasive procedure may lead to intra-uterine infection, despite the procedure being performed in aseptic conditions and the prophylactic use of antibiotics. The most frequent cause of chorio-amnionitis is PPROM with ascending infection, and its presence requires immediate delivery.
- Polyhydramnios which may require more frequent monitoring and possibly an amnioreduction.
- Placental abruption very rarely occurs during intrauterine surgery and has not been observed for FETO.
- Amniotic fluid embolism has never been reported during open or fetoscopic surgery.
- Subsequent fertility.
- Maternal death due to FETO has not been reported. Intensive intra- and postoperative monitoring by experienced obstetric anesthesiologists and perinatologists should allow for early diagnosis and prompt management of such complications as placental abruption, chorio-amnionitis, and amniotic fluid embolism.

Potential Fetal/Neonatal Risks

<u>Risk associated with the diagnosis of CDH:</u>

- Fetal demise. The risk for spontaneous intrauterine death in CDH fetuses identified in the second trimester and managed expectantly is approximately 2%. [42] On the basis of current FETO results, this risk is not increased.
- Morbidity after birth – Babies born with CDH have considerable morbidity from the extensive treatment needed after birth. Examples are bleeding, renal failure, infections, complications during ECMO support; chronic lung disease and pulmonary infections from prolonged mechanical ventilator support, severe gastroesophageal reflux due to the large diaphragmatic defect, failure to thrive due to chronic illness, and complications of prematurity (intra-ventricular hemorrhage, retinopathy of prematurity, sepsis, necrotizing enterocolitis, death).
- Complications of ECMO support – bleeding (neck wound and intraventricular), sepsis, renal failure, and failure to wean.

Risk associated with the FETO Procedure:

- It is possible that fetal intervention would increase morbidity by allowing survival of a severely affected fetus that would otherwise have died, or by successfully treating pulmonary hypoplasia at the expense of complications of a preterm delivery.
- Indomethacin can be associated with significant narrowing of the ductus arteriosus in late gestation. If narrowing occurs, indomethacin will be discontinued.
- Vocal cord injury – Vocal cords may be injured by fetal tracheoscopy. If injury to the recurrent laryngeal nerve or vocal cords is clinically suspected, then bronchoscopy will be performed for confirmation of diagnosis and possible treatment.
- Chorioamniotic separation – Potential sequelae are PPROM, amniotic band syndrome, and umbilical cord constriction with either fetal growth restriction or death.
- No biologic response after tracheal occlusion – This may be due to incomplete occlusion, inadequate occlusion time, or inadequate fetal lung liquid secretion.
- Complications of prematurity – Intraventricular hemorrhage, retinopathy of prematurity, sepsis, necrotizing enterocolitis, resulting in exclusion from ECMO, death
- Complications of fetal tracheal occlusion – Tracheomegaly, which is widening of the pars membranacea, is a relatively constant finding, however, thus far no clinically relevant problems have been documented; vocal cord injury, widening of the trachea/tracheomegaly, tracheomalacia/dyskinesia during respiration, barking cough during respiratory efforts, airway occlusion in event of precipitous delivery. For additional data regarding tracheomegaly, please refer to the following publications [1-3]. No vocal cord injury has been described.
- Procedure failure: The failure rate of entering the uterus or trachea, or positioning the balloon is currently estimated to be 2%. In most cases, this can be anticipated by assessing the fetal position and the degree of amniotic fluid volume. In cases of unfavorable positioning, the case may be postponed or rescheduled for a later date.
- In the European series, neonatal death of 5% was related to difficulties in removal of the balloon and airway occlusion. Importantly, all cases of neonatal death occurred as a

result of difficulty in removing the tracheal balloon outside a FETO center where experience and qualified personnel were not immediately available to remove the balloon emergently. There were no neonatal deaths that resulted from difficulty in removing the occlusion in this series when the procedure was performed in a FETO center. In the current study, all patients will remain within 30 minutes of center through delivery and postnatal care to prevent this complication.

Additional Risks

- Some of the questions asked may make the pregnant woman/mother/father/partner/child uncomfortable or upset
- Some of the testing may upset the child. However, all of the planned tests are part of the routine care for children with CDH with the exception of developmental testing which is a research procedure.
- As with taking part in any research study, some privacy may be lost. All medical records and information will be handled per CHOP guidelines.
- Pregnant women and their fetus will be required to remain within 30 minutes of center between the FETO procedure and the balloon retrieval procedure and this may be inconvenient for the pregnant woman and/or family.
- The parent(s) and child will be required to return to CHOP for delivery, postnatal care and follow-up testing which may be inconvenient for the parent(s) and/or family.

Minimizing Risk

Fetal Risks:

The fetal procedures will be performed by specialists in fetal medicine with extensive experience in fetoscopy and the prenatal and postnatal care of a baby with CDH. In addition, the specialists will be trained by colleagues in Europe who have extensive experience in FETO.

Maternal Risks:

- Maternal infectious complications: prophylactic administration of intravenous antibiotics.
- Complications and side-effects of epidural analgesia (if applied): the procedure will be carried out or under the direct supervision of an expert in this procedure.
- Preterm labor induced by the intervention: prophylactic administration of tocolytics
- Maternal uterine/placental bleeding: ultrasound guidance of trocar insertion to avoid placenta and blood vessels in the wall of the uterus.

- The FETO procedure and neonatal management of the patients will be undertaken with a multidisciplinary team of experts familiar with both pre- and postnatal management of CDH and FETO.

9.3.3 Potential Benefits of Trial Participation

The hypothesis is that prenatal intervention will improve survival (primary outcome measure) and morbidity (secondary outcome measure) in patients with isolated, severe left CDH.

9.3.4 Risk-Benefit Assessment

Severe CDH (O/E LHR of less than 25%) is associated with high rates of mortality (CHOP 1996-2010, mortality 17/22 or 77%) and morbidity. In such cases FETO has been introduced as an alternative to the options of termination of pregnancy and expectant management. There is evidence from experience of nearly 300 cases treated by FETO in Europe that the survival rate is improved. There is also evidence that this increased survival is not at the expense of an increased short-term morbidity. In contrast, survivors seem to have less morbidity than can be expected based on the severity (O/E LHR).

The main risk for the fetus is iatrogenic prematurity, which in this study is minimized by performing the procedure in the third trimester and via fetoscopy. However others have shown that later TO leads to proportionate less lung growth.[43,44] The advantages of an earlier intervention in terms of achievable lung growth must be weighed against the disadvantages of PPROM and early delivery in a limited number of patients.

9.4 Recruitment Strategy

Recruitment and Selection

Patients identified at CHOP or referred to CHOP, who agree to come to Philadelphia, PA for standard of care evaluation during the study period, and are found upon review of their standard of care medical records to be appropriate candidates for the study will be approached for entry into the trial. The CFDT has a long-standing national referral base that will assist in the recruitment of pregnant women/fetuses.

Inclusion of Women and Minorities

All pregnant women, of any race or ethnicity, evaluated at the CFDT with a confirmed fetal diagnosis of severe left CDH will be approached for participation in this study.

9.5 Informed Consent

The diagnosis of a severe fetal anomaly is emotionally charged, and patients often seek prenatal therapy with a desire for intervention.

The attending fetal surgeon will perform the consent procedure at CHOP. The consent procedure will include a face-to-face detailed multidisciplinary discussion of the results of

the prognostic evaluation with the family in a private room. Details of potential options for management of their baby's condition (continue pregnancy and receive standard postnatal care or enter the trial and undergo FETO) will be discussed. The voluntary nature of participation in the study will be explained in detail. A person fluent in the parent's language will assist in consenting women who are not fluent in English. Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol by local oversight.

9.6 Payment to Subjects/Families

The pregnant woman/mother/child will not be compensated for taking part in this research study.

The below information will be reviewed with all subjects before enrollment and is outlined in the study ICF.

CHOP is providing financial support for the study. The study will cover the costs of the following:

- Research procedures related to the screening visit, and weekly check-ups between 27 and 34 weeks, not related to routine prenatal care.
- Travel and lodging will be covered in order for subjects to return for the 6, 12, and 24 month research procedures.

The following procedures will be billed to the subjects insurance. If the subject does not have health insurance or insurance does not cover all the costs, the CFDT staff will discuss payment options with subjects before any study related procedures occur.

- Prenatal and perinatal management. (SOC)
- Pre-operative testing in preparation for surgery, the first surgery (insertion of the balloon) and the 2nd surgery (removal of the balloon), and post-operative care and management. (Research)
- Costs associated for the medical care of a baby with CDH. (SOC)

10 PUBLICATION

Data obtained from this study will be publicly disclosed, whether positive or negative. Whenever possible, data dissemination will occur through presentation at major scientific conferences and/or publication in peer-reviewed journals, and will be complete, accurate, balanced, and timely. The study team will not misrepresent data in these scientific communications.

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APPENDIX

Please refer to attached Appendices.

- Appendix I: Investigational Devices and Relevant Devices for the FETO Procedure
- Appendix II: Device Labels
- Appendix III: EXIT Procedures
- Appendix IV: CHOP CDH Delivery and NICU Guidelines
- Appendix V: Medications Used During FETO Procedure
- Appendix VI: FETO Standard Operating Procedures
- Appendix VII: Special Delivery Unit Patient Identification Card
- Appendix VIII: Sponsor -Investigator Reporting to the FDA