1) Protocol Title

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

Protocol Version Date: 01-08-2021

2) Objectives

The purpose of this phase 2 study is to assess the feasibility and safety of treating severe CDH with Fetal Endoscopic Tracheal Occlusion at the UC Davis Medical Center.

Primary Objectives:

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

Secondary Objectives:

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

3) Background

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

pulmonary hypoplasia (defined as o/e LHR <25%) and those with moderate hypoplasia (o/e LHR 25-<30%) complicated by liver up in the thorax have survival rates under 30% (7).

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

In the past 20 years since the abandonment of hysterotomy for tracheal clip placement, multiple techniques have been attempted (15-18). Multi-port fetoscopic clip placement was abandoned due to technique associated morbidity, premature delivery, and the difficulty of removing the tracheal clips to establish an airway at the time of delivery (19). The development of the detachable balloon allows a fetoscopic approach, which markedly reduces maternal morbidity, and allows removal of the balloon late in gestation prior to the delivery, facilitating establishment of the neonatal airway with limited damage to the fetal trachea (20, 21). The GOLDBAL2 detachable balloon from Balt Extrusion (Montmorency, France) is currently being used in the international fetal community with successful balloon placement and retrieval for fetal CDH. However, the impact on survival in CDH is still being evaluated. International studies in different fetal centers have mixed results with some centers showing benefit of FETO for improved survival and others showing no benefit (17, 18, 22). Currently, there is insufficient evidence to recommend FETO as the standard of care (23). Investigations are still ongoing with multiple institutions in the United States, Europe, and South America participating in the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial (ClinicalTrials.gov, NCT01240057).

JUSTIFICATION FOR INVESTIGATION

The Fetal Care and Treatment Center (FCTC) at the UC Davis Medical Center has been offering a range of fetal interventions since 2016, including open fetal surgery, fetoscopic fetal surgery, and fetal cardiac valvuloplasty and septostomy. The skill set needed to perform FETO is present with our mature team at UC Davis. Dr. Shinjiro Hirose performed and helped develop the FETO procedure with Dr. Michael Harrison at UCSF for 11 years. Additionally, Dr. Hirose has participated in other fetal endoscopic tracheal occlusion trials. The remainder of the UC Davis surgery team has experience and training with fetoscopy as well as

other surgical procedures involving fetal intervention. To ensure the team is adequately prepared to perform the FETO procedure, the team will conduct dry runs in the simulation center, which is done routinely before beginning any new procedure. Patients are requesting consideration of this experimental treatment with increasing frequency when diagnosed with CDH prenatally. The FCTC team desires to be able to offer this procedure to patients that meet criteria.

4) Inclusion and Exclusion Criteria

INCLUSION CRITERIA

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

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

EXCLUSION CRITERIA

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

1. Adults unable to consent
2. Prisoners
3. Multi-fetal pregnancy
4. History of latex allergy
5. History of preterm labor or incompetent cervix (requiring cerclage), short cervix ($\leq$20mm), or uterine anomaly predisposing to preterm labor
6. Psychosocial ineligibility
    - Inability to reside within 30 minutes of UC Davis Medical Center or inability to maintain follow up appointments

- Social work will meet with each patient to evaluate the social situation and support system. Identifiable issues of social instability or compliance with the protocol will exclude her as a potential candidate.

7. Bilateral CDH, unilateral CDH with o/e LHR $\geq$ 25% or unilateral CDH with o/e LHR <25% but liver completely down in abdomen
8. Additional fetal or genetic abnormalities that would impact care after delivery or be known to have an impact on outcome
9. Maternal contraindications to elective fetoscopic surgery
10. Significant placental abnormalities (abruption, chorioangioma, accreta) known at time of enrollment and/or surgery
11. Maternal isoimmunization or neonatal alloimmune thrombocytopenia
12. Maternal HIV, Hepatitis B with positive surface antigen, Hepatitis C with presence of virus in maternal blood due to risk of fetal transmission during the procedure
13. No safe or feasible fetoscopic approach to balloon placement

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

STUDY INTERVENTION COMPLIANCE

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

5) Study Timelines

Study Duration: 48-60 months is estimated to enroll up to 10 patients. Data will be analyzed after delivery of the 10th patient for primary outcomes. Analysis of all secondary outcomes will require that the infants are discharged from the hospital or 180 days post-delivery if still hospitalized.

Participant Duration: The FETO balloon will ideally be in place 4-8 weeks depending on maternal safety for those that meet inclusion criteria. Mothers will need to participate in weekly evaluations during this time and up to delivery. Mothers will be followed until their postpartum discharge appointment. Infants will be followed through hospital discharge, death, or 180 days of life (whichever occurs first).

Study Date Completion December 31, 2027

6) Study Endpoints

Endpoints:

Primary Endpoints:

1. Successful placement of the balloon at gestational age 27w0d – 29w6d; success will be defined as completion with direct visual placement above the carina and confirmation on ultrasound done during the procedure
2. Retrieval will ideally be at gestational age of 34w0d ± 1 week but success will be defined by retrieval prior to delivery, including safe retrieval during an ex-utero intrapartum therapy (EXIT) procedure

Secondary Endpoints:

1. Fetal MRI prior to balloon placement and 2nd fetal MRI at ± 2 weeks of balloon retrieval
2. Fetal ultrasound o/e LHR before balloon placement and immediately prior to balloon removal
3. Delivery (preterm) and associated morbidities
4. Gestational age at delivery
5. Days neonate is on ventilator
6. Oxygen dependency at discharge and how much
7. Type of ECMO needed and how many days
8. Neonatal discharge from hospital or up to 180 days post-delivery if still hospitalized
9. Maternal postpartum discharge and follow-up to determine maternal complications

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. Successful placement of the GOLDBAL2 balloon	1. Placement: Gestational	1. This timing optimizes lung growth in the late canalicular

	age of 27w0d – 29w6d	and early saccular phases of fetal lung growth.
2. Successful retrieval of GOLDBAL2 balloon	2. Retrieval: Gestational age of 34w0d ± 1 week	2. Removal of the balloon prior to delivery is important in order to avoid an EXIT procedure or airway emergency at birth. Ideally this occurs around the 34th week of gestation to optimize lung growth but have the balloon removed prior to delivery. Furthermore, studies demonstrate enhanced lung development when the balloon is removed prior to birth.
Secondary		
1. Fetal lung volume growth on prenatal MRI	1. Fetal MRI done prior to balloon placement and again done ±2 weeks of balloon retrieval	1. Fetal MRI will measure the o/e TFLV at each MRI. Fetal lung growth (difference between 1st and 2nd MRIs will be calculated).
2. Fetal lung growth on prenatal ultrasound	2. Fetal ultrasound done before balloon placement and immediately prior to balloon retrieval	2. Prenatal ultrasound will measure the o/e LHR at weekly visits while the balloon is in place. Fetal lung growth will be calculated as the difference between the o/e LHR pre-balloon placement and the o/e LHR immediately prior to balloon removal
3. Delivery (preterm) and associated morbidities	3. Type of delivery and	3. Preterm delivery is a known risk of the FETO procedure.

	associated morbidities	The type of delivery and any associated morbidities will be analyzed.
4. Gestational age at delivery	4. Delivery	4. Preterm delivery is a known risk of FETO. Gestational age at delivery will be an important marker in this trial of safety and feasibility.
5. Number of days neonate is on ventilator	5. Short-term duration on ventilator or no ventilator required.	5. A ventilator is often needed for babies with the most severe cases of CDH. We will log and analyze the baby's need for a ventilator and compare the duration of that need to the historical duration, with the goal being to reduce the need for a ventilator.
6. Oxygen dependency at discharge	6. Oxygen dependency at discharge and how much	6. Babies with severe CDH often require oxygen upon discharge. We will assess each baby's oxygen dependency and the amount, with the goal being to reduce the baby's need for oxygen upon discharge.
7. ECMO need	7. Type of ECMO needed and for how long	7. ECMO is a routine treatment for babies diagnosed with a severe CDH. If ECMO is used, the type (VA/VV) and the number of days on the ECMO treatment will be analyzed, with the goal being to reduce the need of ECMO.
	8. Discharge from hospital	

8. Survival to hospital discharge or 180 days	or 180 days of life	8. Survival to hospital discharge will be important as this is a proposed benefit of FETO. We will analyze survival at 180 days for those still hospitalized at that time point.
9. Maternal complications (preterm labor, PROM, PPROM, oligohydramnios, polyhydramnios, placental abruption, chorioamniotic separation, chorioamnionitis, and other infection)	9. Maternal postpartum discharge and follow-up (4-6 weeks after delivery)	9. Known maternal complications can occur during the pregnancy and/or at delivery. Upon discharge post-delivery and at post-partum visit, all potential complications will be assessed.

7) Procedures Involved

OVERALL DESIGN

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

SCIENTIFIC RATIONALE FOR STUDY DESIGN

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

SCREENING AND STUDY PROCEDURES

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

Screening

- Maternal demographics
- Inclusion/Exclusion criteria reviewed

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

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

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

Patients who meet all enrollment criteria and who, after receiving appropriate study information, provide their informed consent (as evidenced by a signed informed consent document), will be enrolled in the study and have the FETO procedure for balloon placement performed at 27+0 to 29+6 weeks gestation. Follow up procedures will occur as listed in the **Schedule of Activities** table.

DESCRIPTION OF FETO PROCEDURE

The procedure for deployment of the fetal tracheal balloon will take place between 27 weeks 0 days and 29 weeks 6 days' gestation as per protocol above, after adequate counseling and signed informed consent. The pregnant mother will come with her support person on the day of surgery. She will be admitted to the hospital and, after confirmation of fetal viability, she will have a spinal/epidural placed. Once in the operating room and positioned, ultrasound assessment for fetal positioning will be confirmed. Maternal IV sedation may be given if required. The fetus will receive an intramuscular injection of Fentanyl (5mcg), Atropine (80mcg), and Rocuronium (3mg). The fetal medications can be redosed every 30 minutes as needed during the procedure to ensure minimal fetal movement and adequate fetal anesthesia. After adequate maternal anesthesia, a uterine trocar will be inserted into the uterus. After the uterine trocar is in place, the fetoscope will be inserted through the trocar into the fetus' mouth and the balloon will be deployed once in the correct position in the fetal trachea. The balloon will be inflated with isotonic fluid and detached into the fetal trachea. This will complete the placement portion and the fetoscope will be withdrawn. Ultrasound verification of the balloon placement above the carina will be done prior to procedure completion. Amnioreduction will be done if required and the uterine trocar will be removed. The skin will be closed with an absorbable suture and/or surgical skin glue.

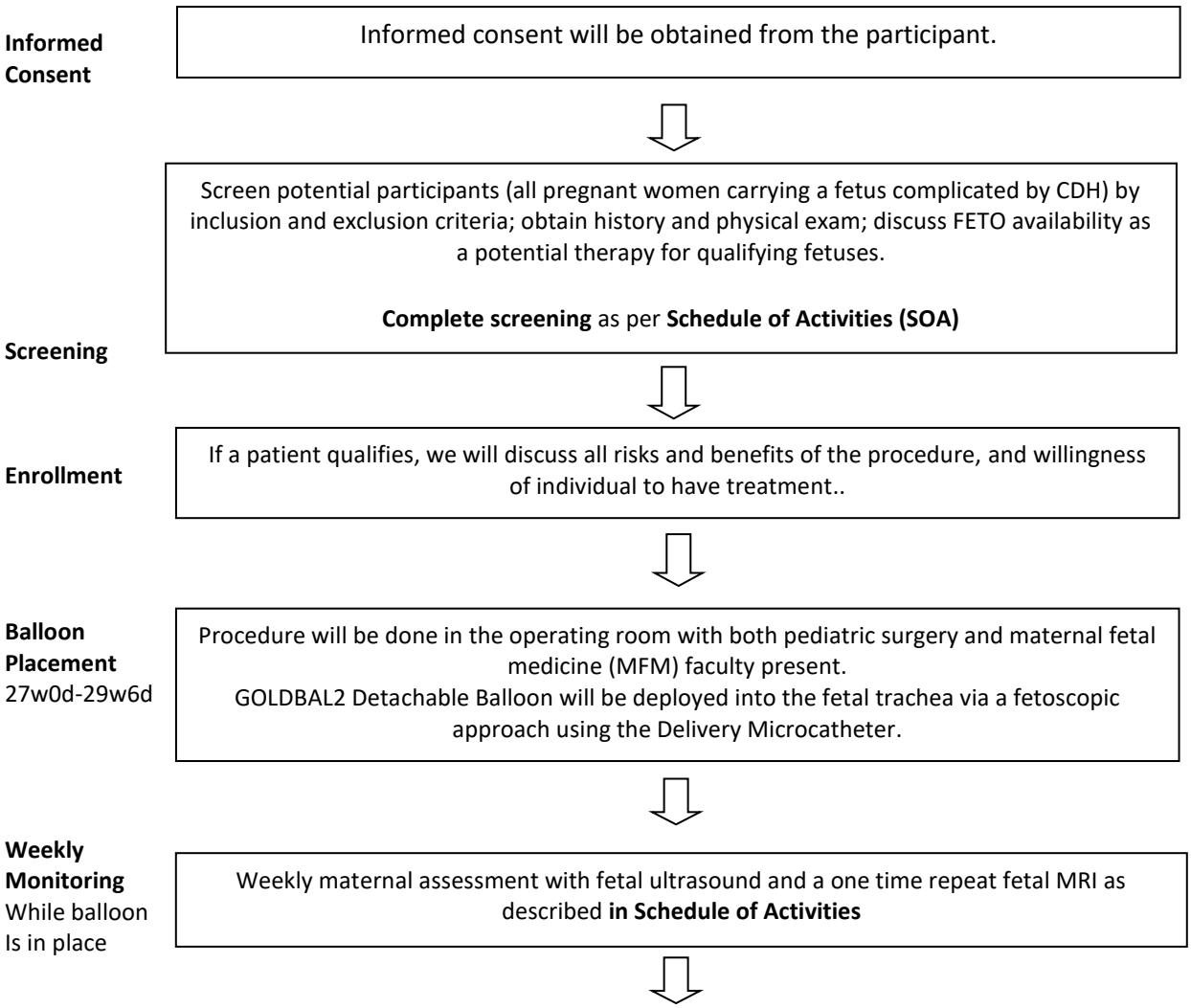
Balloon placement attempt will be defined as trocar placement into the uterus with attempt to gain access into the fetal trachea. We will allow a single uterine trocar placement for each patient for attempted initial placement. If our team fails to place the balloon (surgical failure), this will not be attempted a second time. However, if the balloon is successfully placed and later deflates or is expelled from the fetal trachea (balloon failure), a second attempt will be allowed to maximize benefit to the fetus if this occurs within 10 days of initial insertion and this timing is up to and including 29 weeks and 6 days' gestation. Therefore, a maximum number of balloon placement attempts are: 1 for cases of surgical failure and 2 for cases of balloon failure. There may be cases where the patient is taken to the operating room and, due to suboptimal fetal positioning, uterine access is not attempted. Attempts will be made to externally rotate the fetus into position however if on ultrasound the fetus remains in poor position for balloon placement, uterine access will not proceed. This will not count as a placement attempt and the patient would return to the operating room on subsequent days an unlimited number of times up to 29 weeks and 6 days with the goal of uterine access.

Balloon retrieval will ideally take place between 34 weeks 0 days $\pm$ 1 week. This may occur earlier in select cases for maternal or fetal indications for delivery. All women will receive a course of antenatal betamethasone (12mg intramuscularly every 24 hours for 2 doses) to promote fetal lung development prior to balloon retrieval due to the known risk of preterm delivery. The pregnant mother will again have a spinal/epidural placed. Maternal IV sedation may be given if required. Once in the operating room and positioned, the fetus will receive an intramuscular injection of Fentanyl (5mcg), Atropine (80mcg), and Rocuronium (3mg). Redosing can be done every 30 minutes as needed during the procedure to ensure minimal fetal movement. A uterine trocar will be inserted into the uterus. The fetoscope will be inserted into the fetus' mouth and the balloon will be punctured and retrieved from the fetal trachea. Amnioreduction will be done if required and the uterine trocar will be removed. The skin will be closed with an absorbable suture and/or surgical skin glue. In select cases where fetoscopic intervention is deemed higher risk (e.g. symptomatic polyhydramnios with premature contractions or preterm labor), attempts may be made to puncture the balloon under ultrasound guidance in order to avoid trocar placement into the uterus. The reason for utilizing the percutaneous route secondarily is that the needle decompression is done via ultrasound guidance and not direct visualization. With the percutaneous approach, the needle passes through the fetal neck risking injury to vital structures (carotid artery, internal jugular vein, nerves, etc.). Also, the balloon is not removed and depends on fetal expulsion from the trachea without assurance that balloon remnants do not remain in the fetal airway. Lastly, if the balloon is unable to be retrieved prior to delivery, an EXIT procedure will be planned for safe removal of the balloon prior to birth. These decisions will be made by members of the FCTC team with a multi-disciplinary approach. Potential scenarios requiring EXIT include failure to remove the balloon under other usual means or preterm labor with eminent delivery and inability to remove the balloon by fetoscopic or percutaneous approaches.

After each intervention, subjects will be admitted post-operatively for observation, pain control, and continuous uterine monitoring for contractions. Indomethacin (100mg per rectum preoperatively and then 50mg every 6 hours for 24 hours) will be given with the first fetoscopy to mitigate risk of premature contractions. Prophylactic preoperative antibiotics will also be administered intravenously to mother at the both balloon placement and retrieval to minimize infectious risk (cefazolin 2 grams is preferred;

allergies will be discussed with pharmacy for appropriate substitutions). Maternal pain control will include Tylenol as needed with narcotic medications reserved for breakthrough pain in addition to the spinal/epidural. Length of postoperative stay will be individualized to the patient but is expected to be a 1 night stay for the majority of patients. Upon discharge, the mother and fetus will be followed on an out-patient basis as further described in **Schedule of Activities**. While the balloon is in place, mothers will be followed at least weekly as per standard of care. Weekly ultrasounds will assess for fetal growth, amniotic fluid volume, LHR, o/e LHR, and balloon visualization (when the balloon is in place). After balloon removal, mothers will be monitored weekly for signs of labor. Route of delivery will be based on obstetric indications with vaginal delivery being the preferred approach.

SCHEMA



Balloon Retrieval
34w0d± 1 week

The fetal tracheal balloon will be removed by repeat fetoscopy and retrieval or via percutaneous needle decompression of the balloon under ultrasound guidance (select cases where operative intervention would ensure more risk)

Early retrieval (and percutaneous needle decompression) will be considered for significant polyhydramnios and premature uterine contractions

An EXIT procedure at the time of delivery will be planned if all above fails

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Delivery

Delivery will be determined by MFM faculty regarding best time for delivery of infants with CDH and will be cared for in the NICU with standard therapy given to all CDH babies.

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Hospital Discharge and Follow-Up
Discharge exam and visit within 4-6 weeks of delivery (mom) and at hospital discharge or 180 days of life (baby)

Chart Review and Documentation of all outcomes (primary and secondary)

Schedule of Activities (SOA)

Prenatal Plan							
	Screening	**Enrollment** (within 1 week of balloon placement)	**Balloon Placement** (27w0d to 29w6d)	**Monitoring** (placement to retrieval)	**Balloon Retrieval** (34w0d ± 1 week)	**Monitoring** (retrieval to delivery)	**Delivery**
Maternal Demographics*	X						
Confirmation of diagnosis with comprehensive US including o/e LHR*	X						

Inclusion/Exclusion Criteria Reviewed	X	X					
Maternal History*	X						
Interval Maternal History*		X		Weekly		X	X
Maternal Exam*	X						
Interval Maternal Exam*		X		Weekly		X	X
Counseling with MFM, CGC*	X						
Invasive testing* (Microarray, Karyotype)	X						
Fetal MRI*	X						
Fetal Echocardiogram*	X						
Evaluation with multi-disciplinary team*	X						
Maternal screening for substance abuse and depression*	X						
Maternal labs: CBC, type and screen, antibody screen, HIV, HBV, HCV*	X						
Informed Consent (Study Participation)	X						
Surgical Consent*		X			X		
FETO (balloon placement)			X				
US for fetal assessment including amniotic fluid, membrane status, fetal well-being, o/e LHR*		X		Weekly for remainder of pregnancy (including balloon visualization)		Weekly for remainder of pregnancy	

US includes growth and anatomy overview*				Every 3 weeks		Every 3 weeks	
2nd Fetal MRI (measure lung growth)**				±2 weeks of balloon retrieval			
Additional fetal antenatal surveillance*				Weekly		Weekly	
Balloon retrieval					X		
Delivery*							X
* Standard of Care							

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

**Ideally 2nd Fetal MRI will be done prior to balloon retrieval. In select cases, it may not be able to be completed prior to retrieval and may be done up to 2 weeks after retrieval.

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

DEVICES

Intended Use:

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

FETO Procedure description:
The procedure for deployment of the fetal tracheal balloon will take place between 27 weeks 0 days and 29 weeks 6 days' gestation as per protocol above. Balloon retrieval will ideally take place between 34 weeks 0 days ± 1 week.

Device Descriptions:
General Fetoscopic Equipment:

- Karl Storz Trocar (11650 TG) for uterine access and introduction of cannula (K943713)
- Cook Cannula RCF-10.0 Check-Flo Performer Set (K142829)
- Fetoscopy equipment currently being used at UC Davis per standard of care will also be used

Device and components for balloon placement:

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

Device and components for balloon retrieval:

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

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

All use of the Goldballoon Detachable Balloon (GOLDBAL2*)* will be under the direct supervision of the principal investigator or her designee. The investigational devices will be clearly labeled as investigational

use only. The devices will be stored in the office of the Surgical Care Coordinator in the FCTC at UC Davis Medical Center, with access limited to the study team.

All records of receipt, use, and disposition of the devices will be maintained by the study team. At the completion of the study, there will be a final reconciliation by study personnel of devices shipped, used,

and devices remaining. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused devices.

CONCOMITANT THERAPY

Polyhydramnios is expected while the balloon is in place due to the occlusion of the fetal trachea. This polyhydramnios may cause symptoms of respiratory distress or preterm contractions in the mother. If the polyhydramnios is causing maternal respiratory compromise, without contractions, the FCTC team would evaluate for an amnioreduction in order to improve maternal symptoms. If preterm labor were to occur, steroids may be administered with consideration of tocolysis with or without amnioreduction if indicated. If preterm, premature rupture of membranes (PPROM) occurs, hospitalization for the remainder of pregnancy would be recommended and antibiotics would be considered for prolongation of latency period.

There are cases where the balloon would need to be removed prior to scheduled removal at 34 weeks ± 1 week. Cases will be evaluated on an individual basis but scenarios that are most likely to require premature removal are related to imminent delivery. Maternal reasons for imminent delivery would include medical complications of pregnancy (e.g. pre-eclampsia with severe features or preterm labor not responsive to treatment). Fetal reasons for imminent delivery may include fetal distress. Finally, symptomatic polyhydramnios that is not responsive to amnioreduction or unable to be treated with amnioreduction may be an indication for early balloon removal.

In the extremely rare case of inability to remove the balloon and need for urgent delivery, the FCTC team would plan an ex-utero intrapartum therapy (EXIT) procedure for safe delivery of the fetus. This procedure involves a maternal hysterotomy under general anesthesia with partial delivery of the fetal head and neck. The fetus remains on placental circulation for oxygenation and the balloon will be removed prior to full delivery and removal of the fetus from placental bypass. The FCTC team has experience with this procedure. If an EXIT procedure was unable to be completed or the fetus was unable to be maintained on placental bypass, an emergency airway team is available at all times at UC Davis Medical Center. Emergency bronchoscopy equipment is available to our PCAT (Pediatric Critical Airway Team), and the emergency airway team will be trained in neonatal balloon removal. Emergent neonatal balloon removal will be completed using real time video-endoscopy to remove the balloon and any fragments, suction and clear the airways, and intubate to start ventilation while the cord remains attached to the placenta. The emergency airway team will be taught that if the endoscope is in contact with the inflated balloon, the mucosa may appear flattened and the trachea is being stretched. This will require slight retraction of the endoscope to avoid tracheal injury and allow for balloon decompression and removal. Intent will be for delay of the cord clamping until signs of open and functional airways are present.

8) Data and/or Specimen Management and Confidentiality

☒ I understand that if this study involves the use of the UC Davis Health Electronic Health Record (EMR/EPIC) also contains the clinical data for Marshall Medical Center (MMC). I understand that MMC patient data cannot be accessed for research purposes and that I must take the necessary steps to ensure that MMC data is not accessed, used, or disclosed for UC Davis Health research purposes.

☒ I understand that if this study involves use of UC Davis students' educational records (including records in the PI's own possession such as course exams/assignments), I must consult with the Registrar's office to see if all requirements of the Family Educational Rights and Privacy Act (FERPA) are satisfied.

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

The PI and Co-Investigators (Co-I) will coordinate study activities, identify patients, collect study data, report study results, and ensure the overall safety of the patient. Adequate personnel in the Division of Pediatric Surgery are available to support the conduct of this research. Our Pediatric surgeons and nurses all have extensive research experience in addition to support through the Department of Surgery. The Clinical Research Coordinators and Research Assistants will assist with screening, consenting, enrolling and collecting data for the study. They will assist the PI in adherence to study protocol and deadlines and perform regulatory management. The PI and Co-Is are responsible for proposing and explaining the protocol treatment to the patient for the consent process, performs physical examinations, and monitors test results.

Adequate records will be maintained for the study including subject medical and surgical records, signed ICFs, and device use records. Information collected will be on paper CRFs (Case Report Forms) and will be deidentified, and each patient will have a code that will link them to a separate enrollment excel sheet. This separate excel sheet will contain identifiers that will be password protected and stored on UC Davis encrypted computers.

Protected health information to be accessed for this study includes name, date of births of both patient and baby, medical record numbers for both patient and baby, city and state where patient lives, current hospital medications, outpatient medications, past medical history, diagnoses, test and lab results, all imaging dates (Ultrasounds, MRI, etc.), date of balloon placement and retrieval, dates for when steroids were given, delivery date, and date of baby discharge.

The database that will be used to analyze data is the Research Electronic Data Capture (REDCap) database. The REDCap database will contain information on deidentified patients. REDCap is a secure web application for building and managing online databases for research and for electronic data capture and is HIPAA compliant for data storage. The data received from this trial will be stored indefinitely and banked for future research. The data, after being stripped of any identifiers and coded, will be stored on UC Davis encrypted computers. This data will be downloaded from REDCap once the study is completed, therefore ensuring that it is de-identified, anonymous and accurate.

Only approved researchers to this project will currently have access to the data. The data does not have any patient identifiers. The data set is stored on UC Davis encrypted computers in a secure folder that only approved research personnel for this study has access to.

If this data is needed in the future for a new project, it will only be utilized with a future IRB approved study that appropriately identifies this data set. The PI will send the file through the secure UC Davis email system when the IRB approval for the new study is furnished.

STATISTICAL ANALYSIS AND SAMPLE SIZE

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

GENERAL STATISTICAL CONSIDERATIONS

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

SAFETY ANALYSES

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

9) Data and/or Specimen Banking

All data received from this trial will be stored indefinitely and banked for future research. The data, after being stripped of any identifiers and coded, will be stored on UC Davis encrypted computers. This data will be downloaded from REDCap once the study is completed, therefore ensuring that it is de-identified, anonymous and accurate. A separate enrollment spreadsheet will contain the patient's identifiers and will be stored on encrypted and password protected computers.

Protected health information to be accessed for this study includes name, date of births of both patient and baby, medical record numbers for both patient and baby, city and state where patient lives, current

hospital medications, outpatient medications, past medical history, diagnoses, test and lab results, all imaging dates (Ultrasounds, MRI, etc.), date of balloon placement and retrieval, dates for when steroids were given, delivery date, and date of baby discharge.

Only approved researchers to this project will currently have access to the data. The data set is stored on UC Davis encrypted computers in a secure folder that only approved research personnel for this study has access to.

If this data is needed in the future for a new project, it will only be utilized with a future IRB approved study that appropriately identifies this data set. The PI will send the file through the secure UC Davis email system when the IRB approval for the new study is furnished. If shared with outside institutions, we will only share deidentified data, and only when a data use agreement has been executed. Requests for data will be made to the PI of this trial, and approval must be given before data can be released.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

SAFETY OVERSIGHT

To protect the interests of research subjects and ensure that they are not exposed to undue risk, this trial will be monitored by an independent Data and Safety Monitoring Committee (DSMC). The DSMC will be appointed by the Sponsor-Investigator and shall have no formal involvement with the subjects or the investigation and function independently of Sponsor-Investigator.

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

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

A report will be submitted to the FDA following the delivery of each subject enrolled in the study, to ensure adequate oversight over the safety outcomes.

CLINICAL MONITORING

To assure adequate protection of the rights of human subjects, per 21 CFR 812.40, 812.43 and 812.46, Investigators will conduct continuous review of patient safety. Patients will be monitored weekly during the study. The PI, Co-Is, clinic nurse, clinical research coordinator (CRC), and research assistants will meet at least monthly for protocol specific meetings to discuss patient data and adverse events possibly associated with the study procedures. All enrolled patients will be discussed at these team meetings, which will be held at the University of California, Davis Medical Center. This meeting will update all research staff on the current status of the trial, and any serious adverse events that have occurred will be discussed so that appropriate action can be taken. In between these regularly scheduled meetings, investigators will review and report any serious adverse events in accordance with data safety and

monitoring procedures. All adverse events and serious adverse events will be reported to the UCD IRB according to the current policy.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All adverse events will be recorded on the EMR and eCRFs during study visits and as reported by the participant. The description of the event, date first observed, any action taken, and ultimate outcome will be recorded.
For all adverse events, sufficient information will be pursued and/or obtained so as to permit
1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and;
2) an assessment of the causal relationship between the adverse event and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

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

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

DEFINITIONS OF ADVERSE EVENTS (AE)

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

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

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, an unanticipated life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization of mother, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions after delivery. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they

may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SEVERITY OF EVENT

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

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

RELATIONSHIP TO STUDY INTERVENTION

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

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

procedures, other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

EXPECTEDNESS

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

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.
AEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

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

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

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

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

ADVERSE EVENT REPORTING

All adverse events that occur will be assessed for expectedness and relatedness. Adverse events will be reported to the UC Davis IRB in accordance with their policy.

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

- Death after birth due to CDH disease severity and/or complications of standard of care treatment
- Pulmonary hypertension with resultant need for medications or need of ECMO
- All complications associated with ECMO (i.e. bleeding, stroke, etc.)
- Pulmonary hypoplasia with resultant need for mechanical ventilation
- Gastrointestinal reflux or other feeding problems (i.e. dysmotility, need for feeding tube, etc.)
- Increased oxygenation requirements or need for home oxygen
- Neurodevelopmental delay

SERIOUS ADVERSE EVENT REPORTING

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

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

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

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

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

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions (e.g. CDH in infants) that are already recorded in

the patient's medical history at the time of study enrollment should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

UNANTICIPATED ADVERSE DEVICE EFFECTS

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

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

The Sponsor-Investigator will report all UADEs to the Food and Drug Administration (FDA) within 10 working days after being notified of the event. Thereafter, the sponsor investigator shall submit such additional reports concerning the effect as FDA requests. The sponsor investigator shall also report the results of such evaluation to the UC Davis IRB in the expected time frame of the institution's IRB policy. All UADEs will be reported to the IRB according to local policies and to the FDA according to the regulations found in 21 CFR 812.150.

UNANTICIPATED PROBLEMS

DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the

investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

UNANTICIPATED PROBLEM REPORTING

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

- Protocol identifying information: protocol title and number, PI's name, and the IRB number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported to the UC Davis IRB in accordance with their policy.

PROTOCOL DEVIATIONS

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

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

11) Withdrawal of Subjects

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

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

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

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

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

LOST TO FOLLOW-UP

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

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

- The site will attempt to contact the participant and reschedule the missed visit within 1 week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- In the rare case that the mother is completely lost to follow-up, the study team will contact her referring physician as there is potential for infant risk if the balloon is in place and not retrieved prior to birth or immediately after birth. Instructions on how to retrieve the balloon postnatally will be provided to her home obstetrician.
- All mothers will be given a wallet-sized emergency card with information regarding the balloon and what is to be done in an emergency situation.

Fetal Endoscopic Tracheal Occlusion Trial Participant at UC Davis Health Balloon in fetal trachea. Contact Dr. Shinjiro Hirose in case of an emergency at **916-453-2080**

12) Risks to Subjects

Although FETO has shown increase in fetal lung growth with potential for increased neonatal survival, it does not occur without risks (24). A 2016 systematic review and meta-analysis showed that the most common complications associated with FETO was increased risk of preterm birth (72.4% born before 37 weeks and 17.9% born before 32 weeks) and premature rupture of membranes (46.8% PROM). Less frequent complications were reported as chorioamnionitis (2.6%) and placental abruption (1.2%)(23).

FETO Procedure (balloon placement and retrieval) and/or EXIT Procedure

Maternal risks:

- Premature rupture of membranes (PROM)
- Preterm Premature rupture of membranes (PPROM)
- Preterm labor
- Polyhydramnios
- Amniotic fluid leakage into the abdomen with resultant oligohydramnios
- Chorioamnionitis
- Chorioamniotic separation
- Bleeding with possible need of blood transfusion
- Allergic reaction to latex
- Complications associated with anesthesia/analgesia
- Placental abruption
- Amniotic fluid embolism with resultant respiratory failure

- Deep venous thrombosis that may lead to pulmonary embolism and respiratory failure
- Maternal death
- Need for EXIT procedure

Fetal/neonatal risks:

- Preterm birth with associated complications of prematurity
- Fetal death associated with the removal procedure (inability to remove the balloon)
- Adverse tracheal effects from the balloon including epithelial damage, cartilage and/or muscle damage, tracheomegaly, tracheomalacia, etc.
- Morbidity after birth which may be increased by the procedure as it allowed survival or treated pulmonary hypoplasia at the expense of complications of prematurity
- Failure to enter the uterus/trachea or position the balloon adequately
- Vocal cord injury
- Injury to fetal neck or trachea from percutaneous balloon puncture
- Complications associated with anesthesia/analgesia
- Spontaneous intrauterine fetal demise/death
- Loss of ECMO eligibility (the baby's inability to receive ECMO due to prematurity)

Drug Risks

Indomethacin (given at balloon placement)

Maternal Risk

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

Fetal/Neonatal risk

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

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

Maternal Risk

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

Fetal/Neonatal Risk

- No known risks with single course

Since the inception of fetal surgery, there has been concern regarding maternal wellbeing during the index pregnancy and with future pregnancies (25). A recent survey of women who had undergone FETO versus expectant management for a CDH pregnancy was completed. Although the response rate was only 40%, there was no evidence of worse outcomes for the fetoscopy group. Specifically, no one reported subsequent fertility problems and subsequent pregnancies had the same rate of congenital anomalies or complications as the normal population (26).

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

13) Potential Benefits to Subjects

FETO has shown to increase prenatal lung volumes and prenatal lung perfusion (27, 28). Hypothetically, these will counteract the two major problems associated with CDH, namely pulmonary hypoplasia and pulmonary hypertension. Although individual studies show mixed results, a 2016 systematic review showed increased neonatal survival in severe CDH patients who underwent FETO. Specifically, the relative risk comparing FETO to expectant management was 5.8 (1.5-22.9) for 30 day survival and 10.5 (1.5-74.7) for 6 month survival (23).

ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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

14) Sharing of Results with Subjects

The results of this study will not be shared with subjects, during or upon completion of the study outside of published data results.

15) Prior Approvals

N/A

16) Provisions to Protect the Privacy Interests of Subjects

Patients will be contacted by a member of the research team in a private setting such as a patient room or conference room. The research team will explain the study treatment, procedures, and the timing of each to the patient/family and they will be offered the opportunity to ask questions. Patients' privacy interests will be respected at all times and requests for specific privacy requirements will be met if at all possible, taking into consideration the study protocol requirements and the patients' welfare. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Only research personnel approved by the IRB to work on this project will have access to this study.

Access to medical records that contain patient's personal information for the purpose of this study will be limited to the approved research personnel. These personnel already have knowledge of and access to identifiable medical information of the current patient populations as part of their daily job functions. EMR access PHI is password-protected and no PHI will be reused or disclosed to any other person or entity, except as required by law.

To minimize the risks of breach of confidentiality, we will not include any information that directly identifies the subjects on the information we collect, and on the data resulting from the research. Instead, we will record a code on the information, and we will keep a link between the code and the subject's identity in a different location.

17) Compensation for Research-Related Injury

If subjects are injured as a result of being in this study, the University of California will provide the necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or may be billed to the participants insurance company just like other medical costs. The University do not normally provide any other form of compensation for injury.

18) Economic Burden to Subjects

There will be no cost to the subject for any procedures that are done only for the study such as the second MRI. They will have to pay for basic expenses like any childcare, food, parking, or transportation related to study activities. The subject or their insurance company may be billed for any standard medical care (not part of this study) given.

19) Drugs or Devices

☐ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☒ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

20) Review Requirements

Are there any contractual obligations or other considerations that require IRB review of this research, or review at intervals other than those required by the Common Rule or FDA? If yes, check box:

☐ Yes

☒ No

References

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