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

Investigator: Shinjiro Hirose, M.D.

California Experimental Subjects Bill of Rights

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
- Any common or important discomforts and risks.
- Any benefits you might expect.
- Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
- Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document.

What are my rights when providing electronic consent?

- California law provides specific rights when you are asked to provide electronic consent:
  - You have the right to obtain a copy of the consent document in non-electronic format
  - You have the right to provide consent in a non-electronic format.
  - If you change your mind about electronic consent, you have the right to request your electronic consent to be withdrawn and you can then provide consent in a non-electronic format; however a copy of your electronic consent will be maintained for regulatory purposes. If you wish to withdraw your electronic consent please tell the study team
- This agreement for electronic consent applies only to your consent to participate in this research study.

Key Information about This Research Study

You are invited to participate in a research study. You are invited to be in this study because your fetus (unborn baby) has been diagnosed with severe congenital diaphragmatic hernia (CDH). The purpose of this research is to determine whether the experimental Fetal Endoscopic Tracheal Occlusion (FETO) procedure is effective and safe for treating severe CDH in fetuses. CDH is a birth defect in which there is a hole in the diaphragm (the muscle that separates the chest from the abdomen) of a baby causing the abdominal organs (such as the intestines, stomach, and liver) to enter the chest and weaken lung development. A CDH is considered severe when certain measurements (lung to heart ratio) is lower

than expected (less than 25%) and the baby's liver is located in the chest. Babies diagnosed with a severe CDH typically have a low survival rate. Those that survive will likely have underdeveloped lungs, resulting in difficulty breathing and other associated diseases. We hope to improve this outcome with the FETO procedure, which is meant to promote lung growth. You are invited to be in this study because you are pregnant, and your fetus has been diagnosed with severe CDH. Your participation in this research will involve 10-14 visits and will last about 34-40 weeks. We expect about 10 people at UC Davis to participate in this research. Enrollment in this trial depends upon insurance approval.

Participation in this study will involve the FETO procedure to treat fetuses with severe CDH. FETO is a minimally invasive fetoscopic procedure performed during pregnancy. Minimally invasive means that the number of incisions (cuts) required to insert instruments into the body that are required for surgery will be limited in order to reduce postoperative pain, blood loss, and scarring. A fetoscopic procedure is a technique that allows doctors to obtain information about a fetus during pregnancy. The FETO procedure involves placing a balloon in the fetus' airway, causing a backup of fluid produced by the lungs. As the fluid builds, lung growth and development are promoted. The FETO procedure involves two surgeries: balloon placement and balloon removal. The FETO procedure is only meant to promote lung growth, and the underlying hole in the diaphragm will still need to be repaired post-birth with a standard of care surgery. The procedure involves using the BALT GOLDBAL2 Goldballoon detachable balloon and the BALTACCI-BDPE100 delivery microcatheter, both of which are not FDA (U.S. Food and Drug Administration) approved for the FETO procedure. All research studies involve some risk. Risks of this study are significant. It's important to understand that balloon placement into the baby's airway will not affect the baby's ability to breathe, since babies do not breathe while still in the mother's uterus. However, if the balloon is not removed prior to birth, the baby may die. More of these risks are described in detail later in this document. There is the possibility that you may benefit from participation in this study, but there is also a possibility of the procedure having no effect on promoting lung growth. Long term follow-up appointments will take place annually until 18 years of age at the study site, as per standard of care, regardless if your fetus has the FETO procedure or not.

Here are some reasons you may not want to participate in this research:

- Frequent visits to the research site
- Pain and discomfort at the punctured site
- High risk of preterm delivery

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. If you choose not to take part in this study, your future care will not be affected. If you do not wish to take part in this research study, you will receive treatment according to the standard of care policy and your care will in no way be put at risk. You will not lose any services, benefits, or rights you would normally have if you chose not to participate.

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 and fetoscopic fetal surgery. The skill set needed to perform FETO is present with our experienced team at UC Davis. Dr. Shinjiro Hirose performed and helped develop the FETO procedure. The remainder of the UC Davis surgery team has experience and training with fetoscopy as well as other surgical procedures involving fetal intervention.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions you need to help decide whether or not to join this study.

Information to help you understand research is online at http://www.research.ucdavis.edu/policiescompliance/irb-admin/for-research-participants.

What if I have Questions?

The person in charge of this study is Dr. Shinjiro Hirose. If you have questions or concerns about this study, please contact the Lead Researcher, at 916-453-2080.

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011). This number is a 24-hour number and is available for you to call at any time. Tell the Operator you are participating in a research study and you wish to talk to the on-call Pediatric Surgeon. In the case of an emergency, dial 911 from any phone.

If you have any questions about your rights as a research subject or have complaints about the research study or study team, you may talk to a team member at the Institutional Review Board (IRB) at (916) 703-9158, hs-irbeducation@ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817. The IRB is a group of people who oversee research.

How is this research funded?

This research is being funded by the UC Davis Department of Surgery, also called the sponsor. The sponsor who is overseeing the overall conduct of this trial is the UC Davis Department of Surgery. Sponsors may change or be added.

What happens if I say yes, I want to be in this research?

If you decide to participate in this research study, the researchers will ask you to attend weekly visits at the UC Davis Medical Center and to reside within 30 minutes of the UC Davis Medical Center for the duration of your time in the study The procedures for the research are as follows:

Screening Phase

The screening phase is defined as the time interval between when you sign the informed consent form (ICF) and the time of registration. Some of these activities may have already occurred and are considered standard of care screening activities for evaluating eligibility for fetal intervention. If found eligible to participate in the Clinical Study, you will have the following procedures done:

a) **Informed Consent:** The consent form will be reviewed with you by a member of our care team and you will be given time to read the consent, ask questions, and consider participation. If you choose to participate in this study, you will need to sign and date this form.

b) **Recording maternal medical history:** Standard of care activities that include recording demographic data (date of birth, gender, origin), current and chronic clinical condition, and current medications (including over the counter medicines, vitamins and other health products).

c) **Physical maternal examination:** The physical examination will include measurements of your body temperature, blood pressure, heart rate, and weight.

d) **Fetal ECHO (echocardiogram):** A test that uses sound waves (ultrasound) to evaluate the baby's heart for problems before birth will be done as per standard of care.

e) **ECOG Performance Status:** Your level of functioning in various tasks (ability to care for oneself, daily activity, and physical ability) will be assessed.

f) **Laboratory blood tests:** Standard of care monitoring that includes complete blood count, RH (Rhesus) factor (an antibody screening lab), HIV (Human Immunodeficiency Virus), HBV (Hepatitis B Virus), and HCV (Hepatitis C Virus) tests. The amount of blood taken will be about 2 teaspoons.

g) **Fetal MRI (magnetic resonance imaging):** Scans to produce detailed images of the organs and tissues in the body, known as an MRI, will be done as per standard of care.

h) **Ultrasound:** Imaging used to generate a picture of the inside of the body, typically of a fetus, will be done as per standard of care.

i) **Meeting with healthcare team:** You will meet with the pediatric surgeon, a maternal fetal medicine (MFM) doctor, who is an obstetrics doctor who takes care of high risk pregnancies, as well as a certified genetic counselor (CGC) to discuss various aspects of the study and procedure.

Enrollment Phase

The enrollment phase is defined as the time after you've completed registration and are officially enrolled in the study.

Balloon Placement Phase

The balloon placement phase is defined as the day you are scheduled for the study procedure, between 27 weeks and 29 weeks and 6 days of gestation. The surgical procedure is performed per standard of care guidelines of fetal surgery. This includes a combination of general and epidural anesthesia and details and risks will be reviewed with you by the fetal care surgical team prior to the surgery. The events of that day are detailed below.

a) **Ultrasound:** You will have an ultrasound done prior to surgery. An ultrasound is a type of imaging used to generate a picture of the inside of the body, typically of a fetus. Ultrasound will be used to ensure baby is in an ideal position before beginning the procedure, and to verify the balloon placement. If the fetus is not in an ideal position, your surgery may be delayed to a later date.

b) **Epidural placement:** An epidural (anesthetic) will be given to you prior to beginning the procedure.

c) **Balloon placement surgery:** Surgical procedure done between 27 weeks and 29 weeks and 6 days to insert the balloon into the fetal trachea (airway).

- One hour before the operation you will be given pain killers either orally or through a drip, antibiotics to prevent infection, and medication to prevent contractions. We will also take a blood sample from you (about 1-2 teaspoons) as part of the routine for any operation.

- A thin needle is first passed through your abdomen to give an injection to the fetus for pain relief and to stop any fetal movements. A small cut is then made into your abdomen through which we introduce a thin endoscope (instrument used to look inside of the body) into the uterus. The endoscope is passed through the mouth of the fetus into the trachea. The balloon is passed through the endoscope into the trachea and is left there.
- Balloon placement attempt will be defined as instrument placement into the uterus (also known as the womb) with attempt to gain access into the fetal trachea (airway). We will only attempt initial placement of the instrument into the fetal trachea once. If our team fails to place the balloon (surgical failure), this will not be attempted a second time.
- The operation takes on average 45 minutes to perform but at times, depending on the position of the baby, it may take longer.
- In about 3% of cases, it may not be possible to place the balloon in the correct position or the balloon deflates and a second FETO may be offered after a few days.
- The duration of your stay in the hospital after the FETO will vary from less than a day to a few days depending on your recovery as well as the anesthetic technique used, or the occurrence of unexpected events.

Monitoring Phase I

The monitoring phase I period is defined as the time between balloon placement and prior to balloon removal. Both you and your fetus will be followed closely as follows:

a) **Follow-up:** You will be followed up with members from our Fetal Care and Treatment Center team weekly following the FETO procedure.

b) **Ultrasounds**: An ultrasound is a type of imaging used to generate a picture of the body, typically of a fetus. You will have ultrasounds done at your weekly follow-up appointments in order to monitor the health of your fetus.

c) **Fetal MRI (magnetic resonance imaging):** Scans to produce detailed images of the organs and tissues in the body, known as an MRI, will be done in order to monitor the health of your fetus. If an MRI isn't done in the Monitoring Phase I period, it will be done during the Monitoring Phase 2 period.

d) **Maternal exam:** You will have a routine check-up that may include a blood test (about 1-2 teaspoons), physical exam, vitals, as well as other standard examinations.

Balloon Retrieval Phase

The balloon retrieval phase is defined as the procedure done to retrieve or remove the balloon from the fetal trachea. The details and risks of the surgery will be reviewed with you by the fetal care surgical team prior to the surgery. The events of that day are detailed below.

a) **Ultrasound:** An ultrasound is a type of imaging used to generate a picture of the inside of the body, typically of a fetus. Ultrasound will be used to ensure baby is in an ideal position before

beginning the procedure and to verify complete balloon removal. If the fetus is not in an ideal position, your surgery may be delayed to a later date.

b) **Epidural placement:** An epidural (anesthetic) will be given to you prior to beginning the procedure.

c) **Balloon retrieval surgery:** Surgical procedure done between 33-35 weeks to remove the balloon from the fetal trachea (windpipe).

- We usually remove the balloon in the 35th week of pregnancy (this means 34 weeks till 34 weeks + 6 days). This is done in essentially the same way as the placement of the balloon in the first place. If the fetal position is favourable, it may be possible to puncture the balloon with a needle passed through your abdomen while watching by ultrasound.
- In case of preterm labor and premature birth, the balloon is removed as above or at the latest immediately after birth (again using either an endoscope or a needle).
- If the balloon is unable to be retrieved prior to delivery, an EXIT (Ex Utero Intrapartum Treatment) procedure (specialized surgical procedure used to deliver high-risk babies) will be planned for safe removal of the balloon prior to birth. An EXIT procedure is the delivery of the fetus similar to a cesarean section, with the difference being that the umbilical cord is not cut until an airway has been established to provide oxygen.

Monitoring Phase II

The monitoring phase II period is defined as the time between balloon retrieval and prior to delivery. Both you and your fetus will be followed closely to ensure surgery efficacy. Ultrasounds and an MRI will be performed in order to measure lung growth. Ultrasounds will also be performed to evaluate overall growth. Additional fetal surveillance to assess fetal health and wellbeing will also be conducted.

a) **Follow-Up:** You will be followed up with members from our Fetal Care and Treatment Center team weekly following the FETO procedure.

b) **Ultrasounds**: An ultrasound is a type of imaging used to generate a picture of the body, typically of a fetus. You will have ultrasounds done at your weekly follow-up appointments in order to monitor the health of your fetus.

c) **Fetal MRI (magnetic resonance imaging):** Scans to produce detailed images of the organs and tissues in the body, known as an MRI, will be done in order to monitor the health of your fetus. An MRI will only be done in the Monitoring Phase II period if you did not have one done during the Monitoring Phase I period.

d) **Maternal exam:** You will have a routine check-up that may include a blood test (about 1-2 teaspoons), physical exam, vitals, as well as other standard examinations.

Delivery

The route of delivery will be based on obstetric indications, with vaginal delivery being the preferred approach.

a) **Time and place:** Delivery will be determined by MFM faculty regarding the best time for delivery of infants with CDH and will be cared for in the NICU (Newborn Intensive Care Unit) with the standard therapy given to all CDH babies.

b) **Post-delivery:** You and your baby will be evaluated for discharge.

c) **Baby follow-up:** Your baby will have a follow-up exam at hospital discharge or 180 days of life.

d) **Maternal follow-up:** You will have a follow-up exam within 4-6 weeks of delivery

Prenatal Plan							
Treatment and Schedule of Events	Screening	Enrollment (within 1 week of balloon placement)	Balloon Placement (27 week 0 day to 29 week 6 days)	Monitoring (placement to retrieval)	Balloon Retrieval (34 week 0 day± 1 week)	Monitoring (retrieval to delivery)	Delivery
Administrative Procedures							
Informed Consent (Study Participation)	X						
Inclusion/Exclusion Criteria Reviewed	X	X					
Maternal Demographics*	X						
Maternal History*	X						
Evaluation with multi-disciplinary team*	X						
Interval Maternal History*		X		Weekly		X	X
Maternal screening for substance abuse and depression*	X						
Surgical Consent*		X			X		
Clinical Procedures/Assessments							
Physical Maternal Exam*	X						
Interval Physical Maternal Exam*		X		Weekly		X	X
Counseling with Maternal Fetal Medicine doctor and Certified Genetic Counselor*	X						
Invasive testing* (Microarray, Karyotype)	X						
Laboratory Procedures/Assessments							

Do not write below this line. For IRB stamp and version date only.

Maternal labs: CBC, type and screen, antibody screen, HIV, HBV, HCV*	X						
Radiologic Evaluation							
Ultrasound (to confirm diagnosis) *	X						
Fetal MRI*	X						
Fetal Echocardiogram*	X						
Ultrasound (for fetal assessment)		X		Weekly for remainder of pregnancy (including balloon visualization)		Weekly for remainder of pregnancy	
Ultrasound (for fetal 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 Placement/Retrieval Phase							
FETO (balloon placement)			X				
Balloon retrieval					X		
Delivery*							X
* ***Some procedures listed above may be performed as standard of care at your regular doctor visits, if not, you may be asked to come into the clinic to complete these procedures/tests.***							

Postnatal Plan

Do not write below this line. For IRB stamp and version date only.

	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
**** Some procedures listed above may be performed as standard of care at your regular doctor visits, if not, you may be asked to come into the clinic to complete these procedures/tests.***				

Do not write below this line. For IRB stamp and version date only.

How is being in this study different from my regular health care?

People with fetuses diagnosed with CDH usually don't have any fetal intervention done. Treatments/procedures done to treat CDH are typically done once the baby is born, as per standard of care. If you take part in this study, you would be receiving fetal intervention to treat your baby's CDH prior to birth **in addition** to the standard of care CDH repair surgery that takes place shortly after birth. This study is not part of your standard health care. If you decide not to join the study, your doctor will treat you appropriately according to the best standard medical care available. You can discuss alternative treatments with your doctor who can explain in detail the risks and benefits associated with each alternative approved therapy and discuss the therapy that is appropriate for you. Your participation in this clinical study is entirely voluntary.

Do I have to be in this study? What if I say "yes" now and change my mind later?

No, you do not have to be in this study. Taking part in research is voluntary. You can choose to be in the study or not be in the study. If you decide to be in the study, you can choose to leave the study at any time.

If you decide not to take part in the study, or if you choose to leave the study, your choice will not affect any treatment relationship you have with healthcare providers at UC Davis Health or any services you receive from them. No matter what you decide, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

If you decide to leave the research, contact the study team so the investigator can work with you to create a safe plan for your withdrawal. If you withdraw or are withdrawn from the study after balloon placement and before scheduled removal, you will still require weekly OB/MFM follow-up to ensure safe delivery and you would still be required to deliver at UC Davis or another hospital that is a CDH center to ensure a safe delivery and removal of the device for your infant. If you decide 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 fetal intervention.

If the balloon is already placed and you choose to leave the study, it is necessary to remove the balloon prior to delivery or risk neonatal death. If you decide to leave the study before balloon removal and choose to deliver at a site or hospital not trained in balloon removal, there is a high risk that the fetus may die as a consequence of the site staff not being trained in balloon removal and having difficulty removing the balloon, resulting in a blockage of the baby's airway.

If you stop being in the research, data and specimens that have already been collected will not be removed from the study database. You will be asked whether the investigator can collect data from your future routine medical care. If you agree, this data will be handled the same as research data.

What are my other choices if I do not take part in this study?

You do not have to be in this research study to get care for your fetus' severe CDH. If you decide not to take part in this study, you have other choices. For example:

- You may decide not to get treatment prior to delivery but receive surgery and care following the birth of your child.
- You may choose to get the regular care described above for your fetus' severe CDH.
- You may choose to take part in a different study if one is available.

These options may have risks. Discuss the possible risks and benefits with your study doctor. We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

Can I be removed from the research without my OK?

The researchers may take you out of the study, even if you want to continue, if:

- your health changes and staying on the study is no longer in your best interest;
- you do not follow the study rules or you no longer meet the requirements to be in the study; or
- the study is stopped by the sponsor or researchers.

Is there anyway being in this study could be bad for me?

There are risks to participating in this research. The study doctor and study team will monitor you to see if you are experiencing any harm related to your participation. If you experience any pain or discomfort, you must inform the study team as soon as possible.

What are the risks?

Expected adverse events related to the FETO procedure are:

Maternal risks:

- Preterm labor: probability – high (75%). There is a high chance that you will go into labor early, before 37 weeks of pregnancy.
- Premature rupture of membranes (PROM): probability – moderate (30%). Premature rupture of membranes is when the fluid filled sac surrounding the fetus ruptures before labor begins. This is more commonly referred to as water breaking early. This is a 30% chance this may occur.
- Preterm premature rupture of membranes (PPROM): probability – moderate (47%). Preterm premature rupture of membranes is when the fluid filled sac surrounding the fetus ruptures before 37 weeks' gestational age.
- Chorioamniotic separation: probability – moderate (47%). Normally, there are two membranous layers surrounding the fetus, that are fused together. Chorioamniotic separation is when these two layers separate from one another.

- Polyhydramnios: probability – moderate (47%). Normally surrounding the fetus is an amniotic sac which holds fluid that protects the fetus. Polyhydramnios is when there is extra amniotic fluid in the amniotic sac.

- Amniotic fluid leakage into the abdomen with resultant oligohydramnios: probability – low (5%). There is a chance that the fluid filled sac surrounding the fetus will leak into the mother's belly, resulting in a low volume of total fluid surrounding the fetus (oligohydramnios).

- Chorioamnionitis: probability – low (5%). Chorioamnionitis is when the thin tissue surrounding the fetus, known as the fetal membrane, is inflamed or swollen due to bacterial infection.

- Bleeding (including from the site of instrument insertion) with possible need of blood transfusion (transfer): probability – low (5%). There is a low chance that you may experience excessive bleeding from the procedure itself or from the instruments inserted for the procedure. If this occurs, you may need blood added to your body through a narrow tube placed within a vein.

- Allergic reaction to latex: probability – low (5%).

- Complications associated with anesthesia and analgesia: probability – low (5%). Anesthesia and analgesia are medications that result in loss of consciousness and the inability to feel pain, respectively. There is a low chance that these medications will introduce complications.

- Placental abruption: probability – low (5%). Placental abruption is when the placenta separates from the uterus before childbirth. There is a low chance that this may occur.

- Amniotic fluid embolism with resultant respiratory failure: probability – low (5%). An amniotic fluid embolism is when the fluid surrounding the fetus (amniotic fluid) or other fetus material enters the bloodstream of the mother. If this leakage does occur, it may trigger a harmful reaction from the mother's body.

- Deep venous thrombosis that may lead to pulmonary embolism and respiratory failure: probability – low (5%). Deep venous thrombosis is when a blood clot (a clump of blood that's turned to a solid state) forms in a vein located deep inside the body. This may result in a pulmonary embolism, which is a sudden blockage of blood flow to the lungs, or in other respiratory complications.

- Maternal death: probability – low (5%).

- Need for EXIT procedure: probability – low (5%). An EXIT procedure will be needed if we cannot remove the balloon from the fetus' trachea at the second procedure. In this situation, the trachea is blocked, and if the baby is born in the standard fashion, she or he will not be able to breathe. In order to remove the balloon, a special type of delivery will be performed. This delivery may require an incision on the uterus that will require C-section deliveries for any pregnancies you have at a later date. The EXIT procedure itself requires general anesthesia for the mother using a breathing tube and will also require a breathing tube for the baby at birth.

Fetal/neonatal risks:

- Preterm birth with associated complications of prematurity: probability – high (75%). There is a high chance that the baby will be born before 37 weeks' pregnancy.

- Loss of extracorporeal membrane oxygenation (ECMO) eligibility: probability – high (75%). The life-support treatment uses a pump to perform the functions of the baby's heart (to circulate blood

throughout the body) and/or lungs and is a specialized treatment for babies diagnosed with a CDH. There is a high chance that the baby will be unable to receive ECMO support due to prematurity.

- Morbidity (disease) after birth: Is referring to other illness and infant death prior to their first breath: probability – moderate (47%). Because there is the risk of the baby being born premature due to the procedure, the risk of morbitity increases as well since premature babies are more at risk of contracting diseases.
- Failure to enter the uterus/trachea or position the balloon adequately: probability – moderate (47%).
- Complications of extracorporeal membrane oxygenation (ECMO) support: probability – moderate (47%). The life-support treatment uses a pump to perform the functions of the baby's heart (to circulate blood throughout the body) and/or lungs and is a specialized treatment for babies diagnosed with a CDH. There is a moderate chance that complications associated with ECMO may occur. The risk of ECMO support is associated with a diagnosis of CDH and not with the FETO procedure itself.
- Fetal death associated with the removal procedure: probability – low (5%). There is a low chance that there will be complications in which the balloon is unable to be removed from the fetal trachea, resulting in fetal death.
- Adverse tracheal effects from the balloon including epithelial damage, cartilage and/or muscle damage, tracheomegaly, tracheomalacia, etc.: probability – low (5%). The balloon will be placed in the fetal trachea (windpipe). The balloon may damage the tracheal muscle and cartilage, cause an abnormally wider trachea (known as tracheomegaly), cause a narrowed trachea that makes breathing difficult (known as tracheomalacia), as well as cause other tracheal damages.
- Vocal cord injury: probability – low (5%).
- Injury to fetal neck or trachea from percutaneous (puncturing the needle through the skin) balloon puncture: probability – low (5%).
- Complications associated with anesthesia/analgesia: probability – low (5%). Anesthesia and analgesia are medications that result in loss of consciousness and the inability to feel pain. There is a low chance that these medications will introduce complications.
- Fetal death associated with the balloon removal procedure: probability – low (5%). There is always the possibility that the fetus may die during the procedure due to unforeseen complications.
- Spontaneous intrauterine (in uterus) fetal demise/death: probability – low (5%).
- Need for EXIT procedure: probability – low (5%). An EXIT procedure will be needed if we cannot remove the balloon from the fetus' trachea at the second procedure. In this situation, the trachea is blocked, and if the baby is born in the standard fashion, he or she will not be able to breathe. In order to remove the balloon, a special type of delivery will be performed. This delivery may require an incision on the uterus that will require C-section deliveries for any pregnancies you have at a later date. The EXIT procedure itself requires general anesthesia for the mother using a breathing tube and will also require a breathing tube for the baby at birth.

Expected adverse events related to the drugs used in the FETO procedure

Indomethacin (given at balloon placement)

Maternal Risk

- Dizziness: probability – low (5%).
- Gastrointestinal distress: probability – low (5%). The gastrointestinal tract is a series of hollow organs joined in a long, twisting tube from the mouth to the anus. Gastrointestinal distress may include heartburn, nausea, vomiting, and an inflamed (swollen) stomach lining.

Fetal/Neonatal risk

- Early narrowing or closure of ductus arteriosus (blood vessel in the heart): probability – moderate (47%).
- Possible impact on renal function (kidney condition) due to oligohydramnios (low volume of amniotic fluid – fluid surrounding the baby): probability – moderate (47%).
- Oligohydramnios: probability – moderate (47%). Normally surrounding the fetus is fluid known as amniotic fluid. Oligohydramnios is when there is a lower than average volume of this fluid.
- Decreased responsiveness to postnatal indomethacin (drug used to relieve pain, swelling, and joint stiffness) for closure of persistent patent ductus arteriosus (failure of the blood vessel in the heart to close): probability – low (5%).
- Possible increased risk of necrotizing enterocolitis (disease that affects the intestine): probability – low (5%).
- Possible increased risk of intraventricular hemorrhage (bleeding in the brain) or periventricular leukomalacia (brain injury): probability – low (5%).

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

- Elevated (high) blood glucose: probability – high (75%).
- Allergic reaction causing wheezing, chest tightness, swelling of face/lips/tongue/throat, or seizure: probability – low (5%).
- Infection at the injection site: probability – low (5%).

Fetal/Neonatal Risk

- No known risks with single course

Other risks:

- Premature removal of the balloon: probability – low (5%). There is a chance that, due to fetal or maternal health reasons, the balloon may be removed earlier than intended, resulting in little to no lung growth, and no response to treatment.
- Long term outcomes may be unknown.

Risks of Blood Draws

There may be risks associated with drawing blood and with the insertion of the catheter during blood collections and leaving it in place. Less than 10% may experience pain, bruising, minor bleeding and lightheadedness and less than 1% experience fainting or infection. However, these are regular risks associated with any blood collection, and are not related to the study drug.

Risk of Fetal Echocardiogram (ECHO)

An echocardiogram uses ultrasound, or harmless sound waves, to quickly and efficiently obtain valuable information about the heart. External echocardiogram poses no risks, as it is noninvasive and does not use radiation. Some people may feel uncomfortable having to lie in one position for the test. There may be risks that are currently unknown.

Risk of Ultrasound

Ultrasound imaging has been used for over 20 years. It is based on non-ionizing radiation, so it does not have the same risks as X-rays or other types of imaging systems that use ionizing radiation. Ultrasound imaging is generally considered safe when used prudently by appropriately trained health care providers. Ultrasound energy does have the potential to produce biological effects on the body. Ultrasound waves can heat the tissues slightly. In some cases, it can also produce small pockets of gas in body fluids or tissues (cavitation). The long-term consequences of these effects are still unknown.

Risk of Magnetic Resonance Imaging (MRI)

The MRI procedure uses a powerful magnetic field to generate detailed images of the body. The magnet could move objects within your body that contain metal, such as implants, clips and pacemakers. Tell the doctor if you have any metal items within your body. While no significant risks have been found from the use of MRI scans, you may be bothered by the MRI machine noise and by feelings of being closed in (claustrophobia). Additional risks include the following:

- The MR environment involves a strong, static magnetic field that will attract magnetic objects (from small to large items) that may cause damage to the scanner or injury to the patient. Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile.
- The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation.
- The radiofrequency energy used during the MRI scan could lead to heating of the body. The potential for heating is greater during long MRI examinations.
- There is a low chance (5%) that MRI related complications might occur during the time the balloon is in place, although no reports have mentioned side effects associated to MRI procedures performed on patients implanted with detachable balloons.

There may be risks that are currently unknown**.**

Risks of HIV Testing

Being tested for HIV can make you feel nervous or anxious about the test results. A positive test indicates that you are infected with the HIV virus, but no one knows for certain when, if ever, you will get AIDS or a related condition. Receiving positive results may make you very upset. If other people learn about your positive test results, there might be a risk that you could be treated unfairly or badly, and even have trouble obtaining insurance or employment. To the extent permitted by law, the researchers will keep your test results confidential and will not release them to anyone without your written permission. If you test positive, California law requires health care providers and clinical laboratories to report the HIV test results with your personal identifying information to the local health department.

Risks of Confidentiality

As with all research, there is a chance that confidentiality could be compromised. To minimize the risks of breach of confidentiality, we will not include any information that directly identifies you on the specimens and information we collect, and on the data resulting from the research. Instead, we will record a code on the bio-specimen and information, and we will keep a link between the code and your identity in a different location.

In addition to these risks, this research may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

Will being in this study help me in any way?

We cannot promise any benefits to you or your fetus from taking part in this research. However, potential benefits include improved healthoutcome with improved lung growth. The information collected in this study may also help define treatments that will benefit fetuses with severe CDH in the future.

This study is not a substitute for your regular medical care. You should continue to see your regular medical providers.

Will being in this study cost me anything?

You or your insurance company will be billed for all procedures related to this study. A letter will be sent to your insurance explaining the procedure and requesting coverage of the procedure. If the insurance denies to cover the procedure, you will no longer qualify to receive the FETO procedure and will be ineligible to participate in this trial. Your child will still receive the standard of care surgery to repair the CDH after birth.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

Will I be paid or receive anything for being in this study?

We will not pay you to take part in this study or pay for any out of pocket expenses related to your participation, such as travel costs.

Biospecimens (such as blood, tissue, or saliva) collected from you for this study and/or information obtained from your biospecimens may be used in this research or other research and shared with other organizations. You will not share in any commercial value or profit derived from the use of your biospecimens and/or information obtained from them.

What happens if I am injured or get sick because of this study?

If you are injured or get sick because of this study, medical care is available to you through UC Davis Health, your local provider, or emergency services.

- If it is an emergency, call 911 right away or go to the emergency room.
- For non-emergency issues, you can call the UC Davis Health Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to on-call Pediatric Surgeon.

If you 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 the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about compensation, you may contact the IRB Administration at (916) 703-9151 or HS-IRBAdmin@ucdavis.edu.

What happens to the information collected for the research?

We will do our best to limit the use or disclosure of your personal information, including information from this research study and from your medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Some organizations may be required to inspect and copy your information including the IRB and other University of California representatives responsible for the management or oversight of this study.

We have strict rules to protect your personal information and protected health information (PHI). We will limit who has access to your name, address, phone number, and other information that can identify you. We will remove identifiable information from the data we collect about you. After we remove all of the identifiers, we will place a code on the information. We will maintain your study data on encrypted computers and access to the information will be limited to only members of the research team who need the access to properly conduct the study.

While this study does involve banking the data and/or specimens we collect with your identifiable information (e.g., your name, medical record number, or date of birth) for future use, we may still use

your data or specimens to answer additional research questions or share them with other investigators for additional research. If we do so, we will remove all identifiable information before use or sharing. Once identifiers have been removed, we will not ask your consent for the use of sharing of your data or specimens in additional research.

However, we cannot promise complete confidentiality. If you agree to be in this study, Federal or state laws may permit or require us to show information to university or government officials**.** We may also show your medical records to study monitors, auditors, the IRB, and the FDA. These groups are obligated to maintain your confidentiality. The following is a list of individuals who may access your records:

- Members of the research team
- Offices and committees responsible for the oversight of research
- Personnel who schedule or perform medical tests or procedures, handle accounting and billing, or do other tasks related to this study
- The U.S. Food and Drug Administration (FDA)

If you agree to participate in this research study, a signed copy of this consent document and the privacy authorization form may be filed in your electronic medical record (EMR) and your study participation may be added to your EMR. This information will be used for your care and treatment and for healthcare operations, which may include billing and payment. Federal and state privacy laws give patients the right to access information about their care and treatment contained in their medical record. During this study, you may not be able to access certain information related to this study in your EMR until the study is complete to ensure that the study remains unbiased. If necessary for your care, this information will be provided to you or your physician.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this web site at any time.

We will access protected health information (e.g., your medical record) for this study and you will be asked to sign a separate form, commonly referred to as a HIPAA authorization, to give your permission. Your medical records may become part of the research record. If that happens, your medical records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/legal/privacy/) and in an attached document.

Will I receive any results from this research?

The results from this research will be analyzed all together (including information from all participants) and published in medical journals and presented at medical conferences. You will not receive publications or articles that are published as a result of this research but they may be available to view

on the internet. You will receive the results of all tests performed on your child during the research procedures, including imaging results, blood tests, and motor tests.

Will information or leftover specimens be used for other research?

During this research, the study team will obtain information about you. They will also collect biological specimens from you such as blood or urine. The information and specimens will be used for this research and may also be used for other research studies here at UC Davis. We may also share the information and specimens with other institutions for research. Before using the information and specimens for other research, the study team will remove information that identifies you so the individuals performing the research will not know who the information and specimens came from. We will not ask for additional consent from you to use your information and specimens for the additional research.

May we contact you by e-mail?

We are requesting your email address so we can remind you about appointments and give you updates as required by the study. Email is generally not a secure way to communicate about your health, as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, please contact the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to a Pediatric Surgeon. You do not have to provide your email address to participate in this study. Please initial one of the lines below.

_____ Yes, you may use email to contact me for this study.

My email address is: _____

_____ No, I do not want to be contacted by email.

Do not write below this line. For IRB stamp and version date only.

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	

Do not write below this line. For IRB stamp and version date only.

Signature Block for Children

Your signature documents your permission for the named child to take part in this research.

Printed name of child

Signature of parent or individual legally authorized to consent to the child's general medical care

Date

Printed name of parent or individual legally authorized to consent to the child's general medical care

- ❑ Parent
- ❑ Individual legally authorized to consent to the child's general medical care (See note below)

Note: Investigators are to ensure that individuals who are not parents can demonstrate their legal authority to consent to the child's general medical care. Contact legal counsel if any questions arise.

Signature of parent

Date

Printed name of parent

If signature of second parent not obtained, indicate why: (select one)

- ❑ The IRB determined that the permission of one parent is sufficient.
- ❑ Second parent is deceased
- ❑ Second parent is unknown
- ❑ Second parent is incompetent
- ❑ Second parent is not reasonably available
- ❑ Only one parent has legal responsibility for the care and custody of the child

Signature of person obtaining consent and assent

Date

Printed name of person obtaining consent

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process

Date

Printed name of person witnessing consent process

Do not write below this line. For IRB stamp and version date only.

Optional Data/Specimen Banking Language:
Will information or leftover specimens be used for other research?
We will keep the data we collect about you and we will keep your data and samples for an indefinite period of time.

Keeping data or samples for future research is called "banking." The banked data and samples will be kept in a secure location for use by researchers.

This is what will happen with your banked data and samples:

- We will use the data and samples in other research projects
- The data and samples may be shared with other researchers at UC Davis and with researchers outside of UC Davis.
- The banked data and samples will be labeled with a code instead of your name.
- When we give your data and samples to other investigators for research projects, they will not be able to use the code to figure out which data and samples are yours.
- The research team will maintain a link between your data and samples and your identifiable information kept by the study team.
- You can request to have your data and samples removed from the bank by contacting the research team at any time.

Please initial one of the lines below to indicate whether or not you agree to the optional data and samples banking:

____ Yes, I agree to have my data and samples banked for future research purposes.

____ No, I DO NOT agree to have my data and samples banked for future research purposes.

Do not write below this line. For IRB stamp and version date only.