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MINIMALLY INVASIVE FETOSCOPIC REGENERATIVE REPAIR OF SPINA BIFIDA - A PILOT STUDY

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CO_2	Carbon Dioxide
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
fSBA	Fetal Spina Bifida Apperta
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MMC	Myelomeningocele (Spina Bifida)
PHI	Protected Health Information
PI	Principal Investigator
PPROM	Premature Rupture of the Membranes
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect

Study Summary

Title	Minimally Invasive Fetoscopic Regenerative Repair of Spina Bifida – A Pilot Study
Running Title	Fetoscopic Repair of Spina Bifida

IRB Protocol Number	18-008622
Phase	Pilot
Methodology	Un-blinded, non-randomized, single arm
Overall Study Duration	The investigation is anticipated to take 5-10 years.
Subject Participation Duration	Each subject will be in the study for 60 months.
Objectives	The primary objective is to investigate the feasibility of performing this minimally invasive fetal surgical repair of myelomeningocele (MMC).
Number of Subjects	15
Diagnosis and Main Inclusion Criteria	Pregnant women - maternal age 18 years or older with a singleton pregnancy diagnosed with MMC and evidence of hindbrain herniation.
Statistical Methodology	Descriptive Statistical Analysis

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the procedures described in this protocol, applicable United States government regulations and Mayo Clinic policies and procedures.

1.1 *Background*

Fetal spina bifida is a devastating neurological congenital anomaly characterized by a closure defect of the spinal column. It results from incomplete closure of the neural tube between 22 and 28 embryological days. Its incidence is approximately 1-2 per 1,000 births. It is considered the most common congenital anomaly of the central nervous system that is compatible with life. [(1)]

1. The most frequent form is myelomeningocele (MMC), characterized by the extrusion of the spinal cord into a sac filled with cerebrospinal fluid (CSF), and is associated with lower limb paralysis and bowel and bladder dysfunction.

2. The majority of MMC can be diagnosed with ultrasound during the first and second trimesters, with diagnosis often occurring between 14 and 20 weeks of gestation following maternal serum screening and detailed fetal ultrasound.[2-5]

3. Fetal MMC is usually associated with an Arnold-Chiari II malformation, which includes a constellation of anomalies such as hindbrain herniation, brainstem abnormalities, low-lying venous sinuses and a small posterior fossa. [6-7] This malformation is associated with different degrees of hydrocephalus. The Arnold-Chiari II malformation has well-known deleterious effects on motor, cranial nerve and cognitive functions. [6-7] Postnatally some form of CSF-peritoneal shunt is frequently required, often resulting in a lifelong requirement for monitoring due to the frequent complications such as shunt failure, migration and infection. [6, 8-10]

1.2 *Investigational Device*

This study will use multiple devices for the surgical procedures as part of this investigation. They were introduced into commercial distribution on or after May 28, 1976 and have been determined substantially equivalent to a device in commercial distribution or are otherwise approved for clinical use. These devices may be used off label without trying to support a change in labeling. By nature, this study will be testing the safety and effectiveness of the devices. Additional detailed information about the devices is available in Section 5 of this protocol.

1.3 *Preclinical Data*

Experimental studies using animal models have shown that prenatal coverage of a spina bifida-like lesion can preserve neurological function and reduce or reverse hindbrain herniation.[9, 11-14] These studies suggest a “two-hit” hypothesis in which the ultimate neurologic deficit results from a combination of the failure of normal neural-tube closure (first hit) with secondary spinal cord injury resulting from prolonged exposure of sensitive neural elements to the amniotic fluid (second hit mechanism).[15-16]

Our group developed a technique to treat fetoscopically the spina bifida in a sheep model using intrauterine carbon dioxide as a distension medium in a sheep model. We demonstrated safety and efficacy of this technique in repairing fetal spina bifida. [17]

1.4 *Clinical Data to Date*

1.4.1 Unpublished data:

Using the knowledge and expertise gained with more than 3 years of experience in fetoscopic sheep surgery, our group leading by Dr Michael Belfort (where Dr. Rodrigo Ruano was part of the group before joining Mayo Clinic), in collaboration with a group in Barcelona (Peiro et al [17]), has developed a novel approach for the minimally invasive repair of fetal neural tube defects. This technique has now been employed in 7 human cases in Barcelona, Spain, 1 in Mexico City, Mexico and 1 in Shiraz, Iran showing its feasibility and applicability to the human uterus and fetus, and demonstrating an improved degree of flexibility in terms of access to the fetus regardless of placental location. The technique is designed to decrease the maternal risks of open fetal surgery while maintaining a similar level of fetal benefit as seen in the randomized controlled trial that compared fetal intervention versus postnatal therapy for spina bifida, which was called the MOMS trial. [18]

Our technique employs an open abdomen/closed uterus methodology that allows significantly more flexibility in the minimally invasive portion of the fetal neural tube repair while at the same time allowing a closed skin repair in a similar manner to that employed at Mayo Clinic using an open uterus approach. In the 9 human cases performed in Barcelona, Mexico City and Shiraz there has not been any incidence of maternal premature rupture of the membranes (PPROM) except for 1 case at 35+ weeks. One pregnancy was delivered at 28 weeks (Mexico). The 9 patients have all been delivered by cesarean section and 7 were by elective late term CS (37+ weeks), one was at 35+ weeks because of PPROM, and 1 (in Mexico) was at 28 weeks from preterm labor. All babies have done well except for 1 in Mexico who died from prematurity.

We have shown in 8 human cases that the placode can be satisfactorily dissected free of the skin using micro-scissors and that the skin edges can be successfully undermined fetoscopically. We have shown in 7 of these cases that a patch of bovine pericardium can be placed over the placode and that the patch can be covered with sealant. In the last 2 cases, the skin edges were sutured with a V-loc suture showing that this technique is also feasible.

The technique employs a novel approach to low pressure uterine distention using the same carbon dioxide gas [14, 19-22] that others attempting fetoscopic repair have used, but employing a much lower gas flow rate and pressure. In addition, our technique allows a significantly quicker neural tube repair because of improved access to the fetus, ability to manipulate the fetus into the required position, and superior port placement resulting from the exteriorized maternal uterus. In addition, because of the exteriorized uterus and the superior placement this allows, we require only two access ports and these can be sutured into the uterus allowing a closed seal and minimizing gas leakage. Finally, recent advances in miniature surgical instruments (Storz 1.5 - 3mm surgical sets) allow unprecedented flexibility which enables a full surgical repair to be performed via a fetoscopic approach.

Before considering clinical implementation of fetal endoscopic myelomeningocele closure as standard care, the frequency of complications should be appropriately reduced and results assessed in larger groups over a longer period of time.

1.4.2 Published Clinical Investigations

The recent publication of the NICHD sponsored randomized controlled trial (MOMs Trial [18]) demonstrated clear neonatal benefit of open in-utero fetal surgical repair of MMC. The study showed a reduction in neurological morbidity, especially in terms of decreased severity of hydrocephalus and in degree of hindbrain herniation (relative risk: 0.67; 95% confidence interval: 0.56-0.81, and need for postnatal ventricular-peritoneal shunting (risk relative: 0.48, 95% confidence interval: 0.36–0.64).

Open in-utero fetal surgery is not without risk and the MOMS Trial showed an elevation in maternal-fetal morbidity/risk when compared to the postnatally treated group, including higher risk for chorioamniotic separation (26% vs. 0%, respectively), maternal pulmonary edema (6% vs. 0%), oligohydramnios (21% vs. 0%), placental abruption (6% vs. 0%), spontaneous membrane rupture (46%; RR: 6.15; 95% CI: 2.75-13.78), spontaneous labor (38%; RR: 2.80, 95% CI: 1.51-5.18), maternal blood transfusion (9%; RR: 7.18; 95% CI: 0.90-57.01), and preterm delivery before 34 weeks (46%; RR: 9.2; 95% CI: 3.81 2.19).[18] The reason for the increased incidence of these complications was related to the nature of the open fetal procedure, which involves a multi-faceted invasive approach including maternal laparotomy, large hysterotomy with uterine edge stapling, and open fetal repair of the spina bifida defect that may involve manipulation and exposure of the fetus for a significant amount of time.

Fetal endoscopic surgery has progressed rapidly over the past decades and we are now able to perform a number of intricate procedures inside the uterus with specially designed instruments. These procedures include laser therapy for Twin-twin-transfusion syndrome, fetal cystoscopy and fulguration of posterior urethral valves, release of amniotic bands, and placement of various shunts and balloons inside fetal structures and cavities (peritoneal, pleural, cardiac, and trachea).

Fetoscopy offers a less invasive therapeutic option that could reduce a number of the morbidities (both maternal and fetal) related to open fetal procedures. [21-25] A few animal studies and some clinical human experience with fetoscopic repair of MMC have been reported showing the feasibility of covering the defect with a patch and sealant, or even in performing a full repair. These repairs have been accomplished using at least two (and sometimes more) entry ports through the uterine wall.[20, 25] Kohl et al., in Germany, have demonstrated the feasibility of performing a complete percutaneous fetoscopic repair of MMC using carbon dioxide to distend the uterus and provide a dry working area for the surgeon to perform the repair.[24, 26] These investigators described a two-layer covering

technique using an absorbable patch (Durasis, Cook, Germany) and sutures. However, while they showed that the procedure is feasible; their percutaneous technique with complete two layer surgical closure of the defect using sutures was associated with prolonged operative time and significant maternal and obstetrical morbidities.

The Kohl group used 3 uterine trocar insertions through an intact maternal abdominal wall, each external trocar having a diameter of 5 mm. Their technique also involved multiple CO2 gas infusion ports in order to maintain adequate distension of the uterine cavity for the surgery to be carried out. The frequency of preterm birth and rupture of the membranes using their technique is higher than that observed in those cases that have had open fetal surgery. As a result, the fetoscopic approach as described by Kohl et al, has not been popularized nor accepted internationally.

Their reports however, have stimulated most fetal surgery groups worldwide to explore the potential of a less invasive methodology for fetal neural tube repair and active programs in this regard are ongoing at different fetal centers in the world. There is no question that the field is ready for a less invasive methodology than what is currently available with open fetal repair.

The value of the Kohl experience has been in proving that CO2 insufflation in the uterus is not toxic to either mother or fetus and is well tolerated by both without evidence of fetal or maternal academia. [27] In their 37 procedures, 36 were successful without maternal or fetal complication intra-operatively. In one case acute membrane rupture occurred during the surgery - a not uncommon complication during any fetoscopic procedure regardless of the use of CO2. In a second case, maternal bleeding occurred when one of the trocars was removed after the surgery.

A recent publication by Verbeek et al [28] showed that in fetal endoscopic repair of spina bifida aperta (fSBA), on average, the fSBA group were born at a lower gestational age than the neonatally repaired spina bifida aperta (nSBA) group (median 32 wks [range 25-34 wks] vs 39 wks [34-41 wks]; p=0.001). The fSBA were all operated on by Tomas Kohl's group in Bonn, Germany, while the neonatal repair group were operated on in Groeningen in Holland. The fSBA group experienced more complications (chorioamnionitis 3/13 (23%), premature rupture of the amniotic membranes 11/13 (85%), oligohydramnios 8/13(62%), and infant respiratory distress syndrome necessitating intermittent positive-pressure ventilation 10/13 (77%). [28] In their paper regarding fSBA patients Kohl et al. reported a maternal complication rate from hemorrhage of 19% (3/16). In two of these cases there was minor placental bleeding during the procedure from inadvertent trauma, while in one case one of the trocars was inadvertently placed through an anterior placenta and resulted in heavy placental bleeding. It should be remembered that Kohl et al have employed a technique that utilizes a minimum of 3 trocars and frequently more, and a procedure time of a median of 4 hours (range 5 minutes to 8 hours). Compared to open spina bifida repair in the MOMS trial the complication numbers are high: chorioamnionitis – 23% vs. 3%, PPROM 85% vs. 46%, oligohydramnios – 62% vs. 21%, In terms of neurological function however, Verbeek et al [28] noted better preservation

after fSBA than after nSBA (median motor and sensory gain of two segments; better preserved knee-jerk [p=0.006] and anal [p=0.032] reflexes). [28]

The intra-individual difference in leg muscle ultrasound density was smaller in fSBA than in nSBA infants (mean difference 24, 95% confidence interval [CI] 15-33; p<0.05), which was associated with better preserved segmental muscle function. Verbeek et al [28] concluded that fetal endoscopic surgery is associated with spinal segmental neuroprotection, but that it results in more complications.

To date, I was part of some surgeries performed at Texas Children's Hospital/Baylor College of Medicine. We have performed one initial case that was published in the Obstetrics and Gynecology journal. [29] This case was performed under a Baylor College of Medicine IRB approved protocol investigating the surgical approach prior to becoming aware that an IDE was required. AC is a 25 year old gravida 2 para 1 patient with one prior term vaginal delivery, presented with a fetus who had a known open neural tube defect. She fulfilled all of the requirements for open neural tube repair per the MOMS criteria. Patient AC was originally offered the standard open procedure and consented to the open procedure. She was then (per protocol) apprised of the fetoscopic procedure and she fully understood the procedure and the risks and benefits. She underwent the surgery on 7/30/2014 at 23 weeks gestation. The surgery was uneventful, performed per protocol, and the neural tube defect was closed as expected. There were no complications with the surgery or postoperative course and the patient was discharged to an outpatient facility (Ronald McDonald House) where she remained until 09/03/2014. On that date, at 28-2/7 weeks she presented with ruptured membranes and was hospitalized and managed as for routine preterm premature rupture of the membranes with latency antibiotics (ampicillin and azithromycin). She remained in hospital on bedrest until the baby was delivered by cesarean section (breech presentation) on 9/21/2014 at 30-6/7 weeks because of a fetal tachycardia and non-specific concern for fetal wellbeing. The baby (GC) did well and had Apgar scores of 8 and 9 at 1 and 5 minutes respectively. He did not require any resuscitation and had excellent cord blood gases with a pH of 7.37 and BE of -0.4. . This baby was discharged home on room air and needed a ventriculo-peritoneal shunt.

Most recently, Kohl et al have published his experience considering technique, maternal outcomes and postnatal outcomes. [30-32] The Germany group have demonstrated that fetoscopic repair of spina bifida was safer for the mothers (no cases of maternal demise, spontaneous labor, placental abruption or need for transfusion) with similar postnatal outcomes [Ventriculoperitoneal shunt placement within 1 year was required in 45% of the cases] when compared to the MOMs trial. However, the Germany group has described high rates of premature rupture of the membranes (PPROM) [84.3%, mean gestational age at 29.7 (range, 22.6-37.3) weeks] and prematurity [Mean gestational age at delivery was 33 (range, 24.6-38.1) as they perform the fetoscopic procedure using 5 ports and bigger instruments than our group.

Our group published our experience with 28 patients with 22 patients undergoing fetoscopic repair of spina bifida. [33] We demonstrated that improvement of the surgical technique allowed for better outcomes, leakage of cerebrospinal fluid in 10%, postnatal hydrocephalus in 30%, vaginal delivery in 60% and premature rupture of the membranes in 10%. The outcomes related to the fetus were very similar to the open fetal repair, but with significant reduction of maternal morbidity.

1.5 *Study Rationale and Risk Analysis (Risks to Benefits Ratio)*

1.5.1 Study Rationale

The novel portions of this surgery will be;

1) the approach to the uterus and the use of a minimally invasive technique with CO2 gas within the uterus and 2) a two-three port approach.

In this procedure, the maternal abdomen will be opened via a laparotomy incision and the uterus will be exteriorized with the fetus in-situ. Once the uterus is exteriorized the fetus can be manipulated through the wall of the uterus into an ideal position for the surgery, regardless of the placental location. A small volume of amniotic fluid (+/- 200cc) will be withdrawn through an 18G needle (placed under ultrasound guidance) prior to starting the fetoscopic portion of the surgery, and replaced with carbon dioxide gas at a pressure of less than 20 mmHg. This is sufficient to inflate the uterus to a degree that clearly exposes the fetal back and the spina bifida defect. The PI has participated in at least 10 procedures and the coinvestigator has performed more than 15 procedures now with duration of CO2 gas in the uterus from 1-4 hours without any maternal or fetal complication.

The fetus remains partially submerged in the amniotic fluid and only the back is exposed to the gas. One 12F and one to two 6F-12F vascular access port will be placed in ideal positions for maximal visualization and access. Using standard FDA approved/cleared surgical equipment the neural tube defect will be endoscopically repaired using standard minimally invasive dissection and suturing techniques.

1.5.2 Anticipated Risks

There are a number of maternal and fetal risks associated with the neural tube defect repair procedure.

1.5.2.1 Anticipated Maternal Risks

1. Amniotic fluid leakage into the maternal abdomen, leading to peritoneal irritation. This does not require any therapeutic intervention.

2. Chorioamniotic separation

3. Bleeding (in the absence of placental abruption) can occur from the uterine entry site leading to hemoperitoneum. This is usually self-limited but the patient needs to be monitored closely and if necessary treated with a blood transfusion. Prevention consists of ultrasound-guided insertion.

4. Local wound infection at the trocar and/or laparotomy sites occurs in less than 5% of cases and is managed by the administration of antibiotics and/or local drainage.

5. Regional analgesia can be complicated by postdural puncture headache, failed sensory blockage, infection, hematoma, neurologic injury, and drug side-effects (pruritus, nausea and vomiting, urinary retention, hypoventilation, seizure, hypotension). The incidence of these complications is very low and no different than for other conditions where loco-regional is offered.

6. General anesthesia has known complications including death, brain injury, asphyxia, hypotension and damage to lungs, larynx, pharynx and teeth.

7. Possible side-effects of the drugs commonly used after fetal surgery include: a. Magnesium sulfate - flushing, sweating, muscle weakness, nausea and vomiting, lethargy, blurred vision, excess fluid in the lungs necessitating supplemental oxygen; b. indomethacin - intestinal cramping, decreased amniotic fluid production, and constriction of the fetal ductus arteriosus, nifedipine, hypotension.

8. Preterm labor can be induced by the intervention or by PPROM. Prophylactic tocolysis (first line indomethacin, Magnesium sulfate or nifedipine for breakthrough) will be given at the time of the procedure. The risk for patients going into labor without PPROM or infection is less than 2%.

9. Chorioamnionitis- inflammation of the fetal membranes (amnion and chorion) due to a bacterial infection. Any invasive procedure may lead to intra-uterine infection, despite the procedure being performed in aseptic conditions and the prophylactic use of antibiotics. The most frequent cause of chorio-amnionitis is PPROM with ascending infection, and its presence requires immediate delivery.

10. Placental abruption- very rarely occurs during intrauterine surgery.

11. Amniotic fluid embolism has never been reported during open or fetoscopic surgery.

12. Maternal death due to fetoscopic procedures has not been reported, and while it remains a theoretical possibility, and will be included as a potential outcome in the counseling and consent process, the chances are very small. Intensive intra- and postoperative monitoring by experienced obstetric anesthesiologists and perinatologists should allow for early diagnosis and prompt management of such complications as placental abruption, chorio-amnionitis, and amniotic fluid embolism.

13. Preterm delivery, very preterm delivery, or miscarriage can be induced by the intervention or by PPROM.

14. Procedure failure and/or inability to complete the procedure fetoscopically (resulting in the need for open hysterotomy). The main risk associated with open hysterotomy is uterine dehiscence and rupture in the present pregnancy and subsequent pregnancies. Therefore, those patients who undergo open fetal surgeries with hysterotomy need special prenatal care and must deliver by cesarean section at a maximum of 37 weeks of gestation during the pregnancy. After open fetal surgery, patient must wait for 2 years before getting pregnant again and must have cesarean section deliveries at a maximum of 37 weeks gestation in subsequent pregnancies. In addition, open fetal surgeries with hysterotomy are associated with increased risk of premature rupture of the membranes and prematurity.

15. Pulmonary edema

16. Subsequent infertility

1.5.2.2 Anticipated Fetal and Neonate Risks

1. Preterm premature rupture of the membranes. In the absence of signs of infection, the patients will be managed expectantly with hospitalization, antibiotics and possible tocolysis. If there is evidence of infection then delivery will be expedited.

2. Preterm birth

3. Placental abruption- very rarely occurs during intrauterine surgery.

4. Chorioamniotic separation

5. Chorioamnionitis- inflammation of the fetal membranes (amnion and chorion) due to a bacterial infection. Any invasive procedure may lead to intra-uterine infection, despite the procedure being performed in aseptic conditions and the prophylactic use of antibiotics. The most frequent cause of chorio-amnionitis is PPROM with ascending infection, and its presence requires immediate delivery.

6. Potential sequelae are PPROM, amniotic band syndrome, and umbilical cord occlusion with either fetal growth retardation or death.

7. Indomethacin (if prolonged use, higher than 72 hours) can be associated with significant narrowing of the ductus arteriosus in late gestation. If narrowing occurs, indomethacin will be discontinued. However, indomethacin will be used for 48 hours maximum.

8. Oligohydramnios (decreased amount of amniotic fluid)

9. Anesthesia risks for the fetus include fetal bradycardia and fetal demise. In order to avoid fetal demise, we will monitor the fetal heart function continuously during the entire fetal surgery by a specialized fetal cardiologist.

10. No response to the surgical treatment, or failure to reverse the hindbrain herniation

11. Injury to the fetus from the procedure including organ damage caused by the exposure to CO2 gas

12. Cord tethering (tissue attachments that limit the movement of the spinal cord within the spinal column) which may require later surgery intervention

13. The risk for spontaneous intrauterine death after fetoscopy is NOT increased compared to the risk of spontaneous death in cases managed by the usual standard of care.

14. Risks of the dural patch include:
    a. Hematoma formation (a collection of blood in the area of the patch)
    b. Rejection of the patch by the infant's body (as a foreign material)
    c. Inflammation
    d. Calcification (hardening of the patch)
    e. Delayed bleeding / hemorrhage
    f. Adhesion formation (patch causes tissues to adhere together)

15. Complications arising from preterm birth:
    a. Intraventricular hemorrhage (bleeding in the brain)
    b. Retinopathy of prematurity (damage to the infant eyes)

c. Sepsis (severe infection)
d. Necrotizing enterocolitis (damage to the bowel)

1.5.3 Risk Minimizing Procedures and Activities

1.5.3.1 Fetus

The fetal procedures will be performed by specialists in fetal medicine and neurosurgery. The fetal medicine investigators have extensive experience in fetoscopy. The neurosurgery collaborator has significant experience in postnatal and fetal repair of MMC, and is experienced in the postnatal care of a baby with MMC. This project will be carried out with the help of our fetal intervention, pediatric surgery, neurosurgery and neurology colleagues.

1.5.3.2 Maternal

Maternal infectious complications: prophylactic administration of intravenous antibiotics. Complications and side-effects of epidural analgesia (if applied): the procedure will be carried out or under the direct supervision of an expert in this procedure. Preterm labor induced by the intervention: prophylactic administration of tocolytics. Maternal uterine/placental bleeding: ultrasound guidance of trocar insertion, placement of sutures around trocar ports and direct vision and ability to suture bleeding ports because of the exposed uterus.

1.5.3.3 Confidentiality

We will take all precautions to minimize this risk. Once the consent form is signed subjects will be assigned a study ID # and will be identified by this ID # throughout the study. All data collected will be coded with this study ID # and will be stored on a secure server at Mayo Clinic and will be password protected. Only the Principal Investigator, Co-Investigators, and designated research staff will have access to the link between the study ID and subject identifying information. Any hard copy/paper documentation will be stored in a secured area only accessible by designated research staff.

1.5.4 Risk/Benefit Analysis

Since we are testing the feasibility of the procedure, there is no current data regarding procedure failure. This information will be evaluated. If the procedure is not possible to be performed, an open fetal surgical repair will be performed immediately following the confirmation of the investigational procedure failure using the same maternal-fetal anesthesia. It should be noted that these risks all occur with the current standard open procedure as well.

Even with the inherent risks of surgery, the anticipated benefits of significantly increasing neonatal outcomes and decreasing neonatal and maternal morbidity, outweigh the risks. The

potential benefits to be gained by the subject as a result of participating in this research study could be:

1. The ability to intervene in neural tube defect repair at an earlier gestational age.

2. Decreased neonatal morbidity as a result of reduction of the deleterious intrauterine effects of the spina bifida defect through prevention of CSF loss and nerve exposure during intrauterine life, thus preserving functional ability.

3. Direct improvement of neonatal outcomes by reducing rates of premature delivery related to the highly invasive nature of the current model of open uterine fetal surgery.

4. Direct reduction of maternal morbidity because of shorter hospitalization and decreased rates of uterine rupture and uterine dehiscence.

5. Decreased future morbidity for mothers by eliminating the need for repeat cesarean section and the risk of ruptured uterus in any future pregnancy

The risk to benefit ratio is favorable. A potential benefit to society is the development of minimally invasive techniques and equipment that has the potential to change the face of fetal therapy for indications other than open neural tube defects.

1.6 *Anticipated Duration of the Clinical Investigation*

The investigation is anticipated to take 5 years to enroll the patients to accomplish the objectives of the present study. At Mayo Clinic, Rochester we evaluate approximately 5 to 10 patients per year, and we perform 3-5 procedures per year. We will approach the patients about the present study after multidisciplinary evaluation at our Fetal Center and after the patients elect to proceed with fetal intervention. Then, we will discuss with the patients the present protocol and will offer them the choice to participate. If they consent for the present study, we will perform the fetal surgery and will have the Maternal-Fetal Medicine group following them until delivery.

2 Study Objectives

The primary objective is to evaluate maternal, obstetrical and perinatal outcomes after fetoscopic repair of spina bifida.

This is a pilot study to determine the feasibility of performing the minimally invasive technique in our institution. The choice of 15 subjects is generally consistent with the requirement to evaluate the feasibility of a fetal procedure. If the present study shows that the technique is feasible, then the next step will be to perform a randomized controlled study comparing the efficacy of the technique and open fetal surgical repair of MMC.

2.1 Primary Objective

The primary objective is to evaluate maternal, obstetrical and perinatal outcomes after fetoscopic repair of spina bifida.

Our hypothesis is that this minimally invasive technique is feasible, and that this approach may have the same efficacy as open fetal surgery for MMC, but with significantly less maternal-fetal risk and complications. Both mother and baby will benefit from the surgery. The fetus will have a repaired MMC defect, and the mother will not have a uterine incision. A hysterotomy increases the risk of uterine rupture and requires that all subsequent deliveries are by cesarean section (increasing her risk in all future pregnancies). There is also a decreased risk of PPROM and prematurity. Finally, a vaginal delivery is possible following the fetal surgery if the baby is shown to have a skin covered repair.

2.2 Secondary Objective

We aim to evaluate postnatal outcomes.

3 Study Design

3.1 *General Design*

This pilot study is an un-blinded, non-randomized, single arm Pilot Study, which will be conducted at Mayo Clinic, Rochester, Minnesota.

All procedures will be performed using the same technique, instruments and materials by the same team of people. The minimally invasive technique will be offered to patients carrying fetuses with MMC that meet the inclusion criteria, similarly as those currently in place for open fetal surgical MMC repair in a similar manner to the MOMs trial.[(18) Adzick NS 2011]

Patients will be offered the minimally invasive technique as an option to the open fetal surgical repair of MMC (considered the gold standard). All patients will be closely followed up after the procedure, with weekly ultrasound examinations and consultations. Delivery will be scheduled at the participating center hospital and the infants will be followed-up for 24 months by our research team.

3.2 *Primary Study Endpoints*

The primary outcome measure will be to evaluate maternal, obstetrical and perinatal outcomes after fetoscopic repair of spina bifida progression to a larger study.

To assess and describe the following neonatal outcomes following MMC fetoscopic repair:

- Rate of persistence of CSF leakage from the repaired wound or delayed pseudomeningocele formation
- Rate of need for shunt placement in the first year of life

- Rate of delayed spinal cord tethering at 0-60 months
- Gestational age at delivery
- Long term neurological outcome until 60 months
- Hindbrain herniation

To assess and describe the following maternal outcomes following minimally invasive procedure:

- Short term morbidity including preterm labor, preterm premature rupture of membranes, placental abruption, and abdominal or vaginal bleeding
- Peri-operative complications such as anesthesia complications, edema, wound infection
- Incidence of maternal and obstetrical complications such as oligohydramnios, preterm premature rupture of the membranes, prematurity (<37 weeks), extreme preterm birth (<32 weeks) and comparison to historical controls and our own open fetal surgery cases

3.3 *Secondary Study Endpoints*

Secondary endpoints are related to postnatal outcomes including:

- Successful closure of the spina bifida defect (defined as whether the minimally invasive technique can be technically performed in human patients (success of primary skin closure) by assessing the CSF leakage through the surgical closed defect during 24 hours after birth).
- Frequency of reversal of Chiari malformation
- Presence of clinical hydrocephalus that needs postnatal treatment including ventriculo-peritoneal shunting or endoscopic third ventriculostomy evaluated until the age of 5 years.
- Neurological function evaluated by the lower extremity movements as well as bladder and bowel continence.
- In addition the procedure will be assessed as to whether it prevents loss of functional neurological level during intra-uterine life by fetal lower extremity movements.

4 Subject Selection, Enrollment and Withdrawal

Patients with a baby that has been diagnosed with a MMC and fits the criteria, neural tube defect repair via the investigational fetoscopic repair procedure will be offered at Mayo Clinic, Rochester, MN. The PI and co-investigator fetal surgeons will be the primary contacts and the team who will make the initial assessment of whether the patient is a candidate or not. Patients will be referred to our center from their primary physician anywhere in the country. We will be contacted by the referring physicians to determine whether the patient is a suitable candidate. If this is determined to be the case (after discussion with the referring physician) the patient will be contacted and the proposed surgery and our study will be

discussed. If the patient agrees to participate after full disclosure of the requirements for the study and postoperative care she will undergo a detailed ultrasound assessment performed by the PI or co-investigator fetal surgeons, each of whom is trained to perform the assessment. If, after ultrasound and physical examination, the patient still fits all of the criteria, she will be offered the surgery. Patients who meet the eligibility criteria will be extensively counseled, and those who wish to participate will provide written informed consent for the study.

Sample Size
This pilot clinical trial will only consist of one group and blinding will not occur. Empirically, 15 subjects will provide sufficient power for us to determine the feasibility of the technique and a comparison group with which to compare against our patients who have had open fetal surgery for neural tube repair.

Fifteen pregnant women with a fetus diagnosed with MMC that fits the criteria are eligible. All ethnicities are eligible. Inclusion and exclusion criterion are as follows:

4.1 *Inclusion Criteria*

- Pregnant women - maternal age 18 years or older
- Gestational age at the time of the procedure between 19 0/7 weeks and 25 6/7 weeks
- Singleton pregnancy.
- MMC diagnosis with the upper boundary located between Thoracic 1 (T1) and Sacral 1 (S1).
- Evidence of hindbrain herniation (confirmed on MRI to have an Arnold-Chiari type II malformation).
- Absence of chromosomal abnormalities and associated anomalies.
- Normal karyotype and/or normal chromosomal microarray (CMA) by invasive testing (amniocentesis or CVS). If there is a balanced translocation with normal CMA with no other anomalies the candidate can be included.
- Family has considered and declined the option of termination of the pregnancy at less than 24 weeks.
- Family meets psychosocial criteria (sufficient social support, ability to understand requirements for this study).
- Pregnant subject capable of consenting for their own participation in this study.
- Willingness to undergo an open MMC repair, if necessary
- Parental/guardian permission (informed consent) for follow up of child after birth.

4.2 *Exclusion Criteria*

- Fetal anomaly unrelated to MMC.
- Multiple gestation
- Declined invasive testing for karyotype (amniocentesis or CVS)

- Severe kyphosis (defined as curvature of the spina (vertebras) higher than 30º degree measured by ultrasonography or magnetic resonance imaging).
- Increased risk for preterm labor including short cervical length (<2.0 cm), history of incompetent cervix with or without cerclage, and previous preterm birth.
- Placental abnormalities (previa, abruption, accreta) known at time of enrollment.
- A body-mass index ≥40 at first prenatal visit.
- Contraindications to surgery including previous hysterotomy (whether from a previous classical cesarean, uterine anomaly such as an arcuate or bicornuate uterus, major myomectomy resection, or previous fetal surgery) in active uterine segment.
- Technical limitations precluding fetoscopic surgery, such as uterine fibroids, fetal membrane separation, uterine anomalies incompatible with fetoscopy.
- Amniotic Fluid Index (AFI) < 6 cm if deemed to be due to fetal anomaly, poor placental perfusion or function, or membrane rupture. Low amniotic fluid volume that responds to maternal hydration is not an exclusion.
- Maternal-fetal Rh isoimmunization, Kell sensitization or neonatal alloimmune thrombocytopenia affecting the current pregnancy.
- Maternal HIV, Hepatitis-B, Hepatitis-C status positive because of the increased risk of transmission to the fetus during maternal-fetal surgery. If the patients HIV or Hepatitis status is unknown, the patient must be tested and found to have negative results before enrollment.
- Maternal medical condition that is a contraindication to surgery or anesthesia.
- Patient does not meet other psychosocial criteria, as determined by the psychosocial interviewer using a standardized assessment, to handle the implications of the trial.Maternal hypersensitivity to collagen
- Patient does not have a support person (i.e. Spouse, partner, mother) available to support the patient for the duration of the pregnancy.
- Inability to comply with the travel and follow-up requirements of the trial.
- Participation in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial in a previous pregnancy.

4.3 *Subject Recruitment, Screening and Enrollment*

Recruitment and Selection

Patients identified at or referred to Mayo Clinic, who agree to come to Rochester, Minnesota for standard of care evaluation during the study period, and are found upon review of their standard of care medical records to be appropriate candidates for the study will be approached for entry into the trial.

The PI will serve as the primary contact. Since patients are being referred by their primary physicians, the PI will contact the referring physicians to help determine if the patient is a suitable candidate for open fetal surgery of MMC. Patients with fetuses that have diagnosis of MMC that meets the inclusion criteria of the study will be offered open fetal surgery as part of the prenatal standard. Once the patients elect to proceed with open fetal surgical repair of MMC, the fetoscopic repair of MMC will be offered as an investigational procedure and the patients will be invited to participate in the present project.

Patients will be extensively counseled about the risks and potential benefits of the procedures, as well as the experimental nature of the procedure. They will be also fully counseled about the potential for procedure failure with the fetoscopic approach and the need for converting to open fetal surgery.

In order to prevent coercion, the investigational procedure will be presented to the patient in a manner that is an option and voluntary, if the patient chooses not to participate in the investigational procedure, her clinical care will not be affected. After extensive counseling, the patients who wish to participate voluntarily in the present study will be asked to provide written informed consent. By providing signature on the consent form the patient is authorizing participation of her child in this study.

Inclusion of Women and Minorities
All pregnant women, of any race or ethnicity, evaluated at a Mayo Clinic location with a confirmed fetal diagnosis of MMC will be approached for participation in this study.

4.4 *Early Withdrawal of Subjects*

4.4.1 When and How to Withdraw Subjects

Patients will be withdrawn from the present study if one of the following conditions happens:

- If the Sponsor-Investigator decides is in the participant(s) best interest.
- Failure of subject to adhere to protocol (surgery) requirements.
- Subject decision to withdraw from the study (withdrawal of consent).

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Data collection and follow-up for withdrawn subjects will follow the FDA Guidance Document, “Guidance for Sponsors, Clinical Investigators and IRBs – Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials – http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf

- the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed;
- An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information
- If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100)
- If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

5 Study Devices

Devices used in this investigation are either approved or cleared by the FDA for the intended use or another specified use. This study will not be specifically testing the safety or effectiveness of any particular device. The primary objective of this study is to investigate the feasibility of performing this minimally invasive procedure with acceptable maternal, fetal and neonatal outcomes.

Specific individual device information has been submitted to the FDA under the IDE for which this study is being conducted under. This information will be maintained with the FDA and updated as necessary for this study.

5.1 *Preparation of Investigational Devices*

Devices used in the surgical procedure will be prepared according to standard institutional practice.

5.2 *Packaging and Labeling*

Devices to be used in the investigational procedure will be identified and labeled as such. The following is an example of the label to be used to identify these devices.
"CAUTION – Investigational Device. Limited by Federal (or United States) law to investigational use"

5.3 *Receiving, Storage, Distribution and Return*

5.3.1 Receipt of Investigational Devices

Since the devices to be used in this study are approved marketed devices they will be obtained through normal supply chain procedures.

5.3.2 Storage

Devices will be stored in the original packaging until use. Any devices designed for multiple uses will be disinfected, cleaned and sterilized prior to subsequent use and remain in the sterile packaging until use according to standard institutional procedures.

5.3.3 Device Accountability

Investigational devices will be maintained in the restricted access surgical areas. At routine intervals and at the completion of the study, there will be a reconciliation of devices shipped, devices utilized, and devices remaining. This reconciliation will be logged on the Device Accountability form, signed and dated. Any discrepancies noted will be documented, the sponsor-investigator will be notified and an investigation will be conducted to determine the cause of the discrepancy. Devices destroyed on site will be documented in the study files.

6 Study Procedures

6.1 *Visit 1 – Screening Visit*

The following routine clinical information will be obtained or collected in the Screening Visit as standard of care:

- Demographics/Medical History
- Maternal obstetrical history
- Physical Exam including Vital Signs
- Height & Weight
- Laboratory tests –karyotyping
- HIV & Hepatitis B & C testing if not done clinically already.
- Prior/concomitant medications
- Comprehensive obstetrical ultrasound examination, including documentation of cervical length, gestational age, biometry, confirmation of Arnold-Chiari II

malformation and spina bifida defect, and determination of the anatomic spina bifida lesion level as well as the functional lesion level
- Maternal/Fetal MRI to confirm the diagnosis of MMC, spina bifida defect level and the presence of Arnold-Chiari II malformation
- Fetal Echocardiogram to rule out structural abnormalities;
- Patient Education including: MMC description, prenatal and neonatal development, general expected outcomes and management options
- Clearance for surgery by anesthesia and the obstetrical staff
- Psychosocial evaluation to identify family support and possible confounding social issues
- MMC counseling (including information regarding prenatal and postnatal surgery, management following prenatal surgery

The standard management options of postnatal repair and open fetal surgical repair will be offered to all patients as the first set of therapeutic options and the gold standard. In addition, our group will offer the procedure as an alternative experimental option, with a full explanation of the experimental nature of the procedure, the technical benefits and difficulties, and the risks and potential benefits of the procedure and the limited long term outcomes information.

Those patients who request participation in the present study will be informed that they can, a priori, select a cross-over arm if for any reason the fetoscopic procedure is not possible. They can elect that an open fetal surgical repair of MMC be performed (if MOMs criteria are met) or postnatal intervention. This would allow her to have a significantly less morbid procedure on the uterus than open hysterotomy. In the event that this is not possible an open uterus procedure can be performed. In addition, a standardized packet of information will be provided. This packet contains materials describing MMC and includes materials describing prenatal and neonatal development, general outcomes expected, and management options in pregnancy and the newborn period.

6.2 *Visit 2 – Fetoscopic Procedure to Repair MMC*

The procedure will be performed between 19 0/7 and 25 6/7 weeks at the Mayo Clinic, Jacobson Building, Rochester, Minnesota.

Maternal-Fetal anesthesia:
This procedure will be performed under general anesthesia with placement of a maternal epidural catheter for postnatal analgesia management. This is the same anesthesia approach currently in use for open fetal surgeries. The rationale for using the same anesthetic technique for this minimally invasive procedure and for open fetal surgical repair of MMC is to allow moving to open fetal surgery in those cases where the fetoscopic procedure cannot be performed. This will also provide adequate fetal anesthesia during the procedure.

Prophylactic Tocolysis and antibiotics:
Prophylactic tocolysis will be used in all patients with a protocol employing indomethacin 25mg Q6 for 24 hours and nifedipine 10 mg Q6 for 24 hours. If regular, significant, uterine

contractions are observed, therapeutic tocolysis will be started with magnesium sulfate – 6 gram IV loading dose followed by a 2 gram/hour continuous infusion. Prophylactic antibiotics will also be used during the procedure using Cephalexin 1 g IV immediately before the procedure. Nafcillin will be injected into the amniotic cavity at the conclusion of the procedure. Steroids for lung maturity: steroids for fetal lung maturation will be given between 24 and 25 6/7 weeks (two doses of 12 mg betamethasonegiven 24 hours apart, with the last dose given 48-72 hours before the procedure.

Minimally invasive procedure:
We will use a standard laparotomy approach that we currently use in our open fetal surgeries. This involves a transverse lower abdominal skin incision and exposure of the rectus sheath with entry into the abdomen through a vertical or horizontal fascial incision. Once the maternal belly is opened the uterus is exposed and ultrasound is performed to determine the position of the fetus. If necessary, the uterus will be exteriorized and the fetus will be gently repositioned using external version techniques under ultrasound guidance in order to have the fetal back facing upwards (when the mother is supine). A small volume of amniotic fluid (+/- 200cc) will be withdrawn through an 18G needle (placed under ultrasound guidance) prior to starting the fetoscopic portion of the surgery, and the amniotic fluid will be replaced with carbon dioxide gas at a pressure of less than 20 mmHg. A 9-12 Fr (Cook Medical, Inc., Indiana, USA) or Step™ Short 5 mm (Covidien, Massachusetts, USA) cannula will be introduced into the amniotic cavity by Seldinger technique under ultrasound guidance, and sutured in place with a through and through vicryl stitch that will plicate the fetal membranes and prevent extension of membrane separation.

The pediatric cystoscope (Karl Storz, Tuttlingen, Germany or Richard Wolf Medical Instruments Corp, Illinois, USA) will be placed into the uterus via this port. An additional 610F port will be added under vision and sutured in place as described. The Storz instruments (graspers, scissors, and needle drivers) will be used via these ports to perform the surgery. If necessary additional amniotic fluid will be removed under direct vision and replaced by carbon dioxide at the lowest pressure that will enable adequate visualization of the defect and surrounding skin (< 20mmHg). The maximum insufflation pressures used by Kohl et al ranged from 9 mmHg to 25 mmHg with a median of 17 mmHg). The fetus will be “floating” in the amniotic fluid with the spina bifida lesion exposed to the gas medium. A humidifier (Insuflow, Lexion Medical LLC, St. Paul, Minnesota, USA) will be used during the fetoscopic procedure in order to maintain the chorion-amniotic membranes intact and wet. Because of the unique circumstances of the laparotomy and exteriorized uterus, the access ports can be placed distant from the placenta in order to minimize the chances of abruption of the placenta.

The meningomyelocele sac will be opened at the interface of skin and membranes with the micro scissors to free the placode from the membranes circumferentially. The placode will be allowed to descend into the lesion leaving the skin edge above. A piece of dural substitute material (Medtronic Durepair regeneration matrix, Medtronic, Oakland, NJ, USA) will be cut to the size of the meningomyelocele defect, introduced through a port using a grasper and laid on top of the placode without any suture. The main reason for placing a piece of dural

substitute material over the placode is to thicken the repair and prevent cord tethering and CSF leakage. The skin edges will be primarily opposed and sutured together using standard surgical technique with barbed 4/0 (Covidien,V-loc or Ethicon Stratfix) suture. If skin closure is not possible using the available skin, relaxing incisions will be made using micro scissors 1-2cm lateral to the defect to allow a primary skin closure. If primary skin closure is not possible after relaxing incisions are made, the uterus will be opened and the procedure completed with a sewn in patch of AlloDerm (Life Cell Corp. Branchburg, NJ) using an open technique.

Before removing the trocar, the gas will be removed through the port and the amniotic fluid will be replaced by lactated ringer.

6.3 *Weekly postsurgical visits – Postsurgical Management before delivery (V3 follow-ups)*

The expected hospital course is 96 hours; however, it is possible that the patient will be hospitalized for complications or preterm labor. The patient will then be discharged to nearby accommodation for long term stay until delivery (usually Ronald McDonald House in Rochester, Minnesota) Patients will be on modified bed rest for the first 2 weeks post discharge, but will subsequently be allowed to graduate to moderate activity if the uterus is quiescent.

Patients will return on a weekly basis for fetal ultrasound examinations and consultations. Targeted ultrasonography will be used to evaluate the functional neurological level (as shown by lower extremity motility), the posterior ventricles, the Arnold-Chiari II malformation, amniotic fluid level, & membrane status (weekly). Fetal Surveillance by biophysical profiles and Doppler studies will begin at 34 weeks In addition a monthly comprehensive ultrasound examination will be performed and an MRI will be repeated at 30-32 weeks of gestation.

6.4 *Delivery (V4)*

If MRI at 30-32 weeks shows that skin is covering the defect, and that there has been reversal of the Chiari malformation, the patient will be delivered according to obstetric principles which include the option of a vaginal delivery. Cesarean section will only be performed based on obstetrical need. This is a major benefit of the fetoscopic procedure, and has long standing implications for the obstetric future of the mother. Not only will she avoid the risk of uterine rupture in the current pregnancy, but she potentially a cesarean section for the delivery of the current baby and for all subsequent pregnancies. This will lower her risk of hemorrhage and death in the current pregnancy, and will decrease her risk of placenta accreta in subsequent pregnancies.

6.5 *Postnatal Follow-up Visit (V5)*

The infants will be followed-up by the pediatric neurosurgery service. At birth, a physical examination of the child will be performed to evaluate the spine, the spina bifida defect and the need for postnatal MMC surgical repair. In addition, cranial ultrasound will be performed in order to evaluate the baby for evidence of ventriculomegaly, presence of hydrocephalus and an Arnold- Chiari II malformation.
The following information will be collected between birth and discharge:

- Physical Exam – Evaluate spine, the spina bifida defect and need for postnatal MMC repair
- Urologic Assessments – ultrasound of the urinary tract and voiding cystourethrogram (VCUG)
- Cranial Ultrasound – Evaluate for evidence of ventriculomegaly presence of hydrocephalus and Arnold-Chiari II malformation

If there is progressive hydrocephalus, the infant will be treated by pediatric neurosurgery with either a shunt or endoscopic third ventriculostomy. We will also perform motor examination of the legs and anal sphincter response.

6.6 *Long-Term Follow-Up, 12 Months of Age (V6)*

Infants will be monitored clinically for hydrocephalus at 3-month intervals for the first year. At 12 months of age, all children will be evaluated with physical, urologic and neurologic examinations as well as routine developmental testing as is standard for babies with postnatal spina bifida repair. The 12-month examination will include urodynamic test, imaging of the spine to determine the anatomical level of the lesion and magnetic resonance imaging of the head and spine.

- Urologic Assessments – ultrasound of the urinary tract at 3-month intervals for the first year and urodynamic testing at 3 and 12 months of age
- Developmental Testing – Bayley Scales of Infant and Toddler Development™ (3rd edition) Screening Test
- MRI of head and spine

- Cranial Ultrasound – obtain at 3-month intervals for the first year and at 12 months of age

6.7 *Long-Term Follow-Up, 60 Months of Age End of Study (V7-V10)*

All children will be evaluated at 24, 36, 48 and 60 months of age with physical and neurologic examinations. Additional assessments will be completed at each visit as specified below:

Visit 7 (24 months of age):

- Urologic Assessment - ultrasound of the urinary tract

- Developmental Testing - Bayley Scales of Infant and Toddler Development™ (3rd edition) Full Test

Visit 8 (36 months of age):
- Urologic Assessments – ultrasound of urinary track and urodynamic testing
- Developmental Testing - Bayley Scales of Infant and Toddler Development™ (3rd edition) Full Test

Visit 9 (48 months of age):
- Urologic Assessment - ultrasound of the urinary tract
- MRI of head and spine

Visit 10 (60 months of age):
- Urologic Assessments – ultrasound of the urinary tract an urodynamic testing
- MRI of head and spine

The study will conclude at the 60-month visit and in those cases where the patient does not return to Mayo Clinic for the clinical follow-up visits, we will request the medical records from the institution that the patient was seen at and collect the follow-up data from the medical records. All patients will be asked to sign a medical record release to allow this to occur.

6.8 *Unscheduled Visits*

Pregnant women who have undergone fetoscopic repair of MMC and have any complications such as preterm contractions, PPROM, signs of infection, vaginal bleeding will be treated as usual standard clinical care. Additional unscheduled visits will be performed depending on maternal symptoms and signs as part of the standard prenatal care. Any required emergency or unscheduled care will be treated by staff at Mayo Clinic. All visits will be recorded.

6.9 *Schedule of Events Table*

	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Study Activity	**Screening**	**MMC Feto-scopic surgery**	**Weekly PostSurgical Visits**	**Delivery**	**Postnatal Follow Up**	**12 Mo. of age**	**24 Mo. of age**	**36 Mo. of age**	**48 Mo. of age**	**60 Mo. of age**
Visit Window						***+/- 2 months***	***+/- 2 months***	***+/- 2 months***	***+/- 2 months***	***+/- 2 months***
Consent	X									

History	X	X	X	X	X	X	X			
Physical Exam	X	X	X	X	X	X	X	X	X	X
Neurologic Exam					X	X	X	X	X	X
Fetoscopic Procedure		X								
Weekly Fetal ultrasound			X							
Case Report Forms	X	X	X	X	X	X	X	X	X	X
Weekly Doppler Studies			X							
Urology Follow-up					X	X	X	X	X	X
Monthly Comprehensive Ultrasound			X							
MRI			X*			X			X	X
Cranial Ultrasound					X**	X				
Developmental Testing						X	X	X		
Concurrent Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Serious Adverse Events		X	X	X	X	X	X	X	X	X

** = at 30-32 weeks only*
** = Hydrocephalus monitoring every 3 months during the first year of life

7 Statistical Plan

7.1 *Sample Size Determination*

This pilot clinical trial will only consist of one group and blinding will not occur. Empirically, 15 subjects will provide sufficient power for us to determine the feasibility of the technique.

7.2 *Statistical Methods*

Descriptive Statistics

Descriptive statistics (e.g., mean standard deviation, median, minimum and maximum for numerical data and counts and percents for categorical data) will be calculated, as appropriate for all variables. Baseline values for demographic, clinical, and outcome variables (primary and secondary) will be described.

All pregnant women/fetuses entered into the study at Visit 1 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study procedures will be summarized. SAEs (if any) will be described in detail.
AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

Handling of Missing Data

Missing data will be addressed using last observation carry forward (LOCF) where appropriate. Where LOCF is not appropriate missing data will be left as missing. Heavy tailed distributions and outliers will be addressed by considering transformations to allow approximate normality of the means. Data will be reviewed for outliers before analysis and values may be checked against source data.

Multiplicity

For both the primary analyses, and the secondary analyses, there will be one primary (or first) analysis and thus no correction will be made for multiple comparisons. A sequence of outcomes of interest will be described for each analyses, and significance will be assessed in the order of these sequences. Therefore, testing involves closed testing procedures that protect the probability of falsely rejecting the null hypothesis. If a test fails to be significant, then further tests will be calculated in an exploratory rather than inferential manner.

7.3 *Subject Population(s) for Analysis*

All subjects who are consented and intended to be treated will be included in the analysis.

8 Safety Management and Adverse Events

The initial Safety Outcome criteria will be considered to have been achieved for the planned 15 subjects if;

- Fewer than one (1) maternal SAE ≥ Grade 4 as defined by CTCAE and determined to be “probably” or “definitely” related to the procedure. (Examples: maternal Grade 4 event such as (i) maternal death as a result of the investigational procedure, (ii) a life threatening event (risk of death) as a result of the investigational procedure.)

- Fewer than one (1) fetal SAE ≥ Grade 4 as defined by CTCAE and determined to be “probably” or “definitely” related to the procedure. (Examples: (i) death as a result of

the investigational procedure, (ii) a life-threatening event (risk of death) as a result of the investigational procedure.)

- Fewer than one (1) obstetrical SAE ≥ Grade 4 as defined by CTCAE and determined to be "probably" or "definitely" related to the procedure. (Examples: obstetrical Grade 4 event = premature rupture of the membranes, fetal grade 5 event = placental abruption)

- Any clinically indicated MRIs obtained in the interim between study required and standard of care MRI intervals will be reported as an adverse event to the IDE.

All adverse events occurring during the study, including those not meeting the criteria of an Unanticipated Adverse Device Effect (UADE) will be recorded on the appropriate case report form. Records of these events will be maintained and reports submitted to the FDA and IRB according to the regulatory requirements. Expected clinical adverse events and nonsignificant (not serious) clinical adverse events will be reported. Expected clinical adverse events and anticipated adverse device effects are those listed in Section 1.5.2.

8.1 *Stopping Rules*

Trial Stopping Rules: The trial will be voluntarily placed on hold for the following reasons until the FDA, Sponsor-Investigator and the DSMB (see Section 8.7.1) evaluate the safety of the trial and address any required changes to the investigational plan to decrease risk and improve safety:

- if there is one (1) maternal SAE ≥ Grade 4 as defined by CTCAE following the investigational procedure, and determined to be "probably" or "definitely" related to the procedure
- if there is one (1) fetal SAE ≥ Grade 4 as defined by CTCAE the investigational procedure, and determined to be "probably" or "definitely" related to the procedure.
- if there is one (1) obstetrical SAE ≥ Grade 4 as defined by CTCAE the investigational procedure, and determined to be "probably" or "definitely" related to the procedure. (Examples: obstetrical Grade 4 event = premature rupture of the membranes, fetal grade 5 event = placental abruption)

8.2 *Clinical Adverse Events*

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

8.3 *Definition of an Adverse Event*

An adverse event is any untoward medical occurrence in a pregnant woman and/or /fetus who has received an intervention (drug, biologic, or other intervention). The occurrence does not

necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or intervention, whether or not considered related to the medicinal product or intervention.

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

8.4 *Definition of Unanticipated Adverse Device Effect (UADE)*

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

8.5 *Definition of a Serious Adverse Event (SAE)*

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

- Death as a result of the Investigational Procedure
- A life-threatening event (at risk of death at the time of the event),
- **Requires inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability/incapacity, or
- A congenital anomaly/birth defect in the offspring of a pregnant woman related to the procedure.

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

**For this study, it is recognized that inpatient hospitalizations are not uncommon for pregnant women. Standard obstetrical clinical practice generally requires women to be hospitalized for observation and fetal monitoring whenever possible symptoms of preterm labor, preterm premature rupture of membranes, infection, or any other symptoms related to pregnancy may occur. Therefore, every hospitalization incurred by participants in this study will not be considered a Serious Adverse Event (SAE). Each hospitalization will be individually assessed by the Principal Investigator as to whether the reason for the hospitalization meets criteria for a SAE. All pregnancy complications will be collected as Adverse Events during this research study.

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

8.5.1 Relationship of SAE to study device or other intervention

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

Definitely – the event follows in a reasonable temporal sequence from the study intervention and the event cannot be explained by the subject's medical condition or other therapies

Probably – there is temporal relationship between the event and study intervention or the relationship is suggestive and the event is unlikely to be explained by the subject's medical condition or other therapies

Possibly – there is some temporal relationship between the event and the study intervention and the event is less likely to be explained by the subject's medical condition or other therapies

Unlikely – there may or may not be some temporal relationship between the event and the study intervention and the event is more likely to be explained by the subject's medical condition or other therapies

Unrelated – the event is due to an underlying or concurrent illness or effect of a concomitant therapy and is not related to study intervention (e.g., there is no temporal relationship to the study intervention, or has a much more likely alternative etiology)

8.5.2 Severity of Adverse Events

The sponsor-investigator will use the following NCI CTCAE v5 definitions to grade the severity of each AE:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated. **Grade 5** Death related to AE.

Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.5.3 Eliciting Adverse Event Information

Adverse events will be captured through medical record review, self-report, physician evaluation, non-directive questioning during study visits, and/or clinical or research tests. See Section 1.5.2 for a list of potential maternal and fetal complications as a result of the study intervention.

8.5.4 Recording Adverse Events

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

SAEs will be documented as specified above and the relationship of each SAE to the study intervention will be characterized as outlined in Section 8.5. The SAEs and UADEs will be closely followed and any changes in severity (improving or deteriorating) will be documented until resolved.
At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Study subjects will be routinely questioned about adverse effects at study visits. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of the treatment group if applicable or suspected causal relationship to the investigational device

or if applicable other study treatment or diagnostic product(s) will be recorded in the subjects' case history. For all adverse effects sufficient information will be pursued and or obtained as to permit; an adequate determination of the outcome, an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable other study treatment or diagnostic product. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

Causality and severity assessment
The sponsor-investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or other study treatments; and 3) if the adverse effect meets the criteria for a serious adverse effect.

If the sponsor-investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the adverse effect will be classified as associated with the use of the investigational device or other study treatments for reporting purposes. If the sponsor-investigator's final determination of causality is "unknown but not related to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case history.

8.6 *Adverse Event Reporting*

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

8.6.1 Adverse Event Reporting Period

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

For any maternal, fetal or neonatal deaths or other life-threatening events associated with the study intervention:

- Promptly complete an Adverse Event Report

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

Maternal events: Stroke, drug allergy, uterine rupture, pulmonary embolus, ascites, spinal headache from epidural placement, amniotic fluid embolism, hemorrhage that requires blood transfusion or laparotomy, chorioamnionitis, pulmonary edema requiring diuretics or intubation, complications of general anesthesia, magnesium toxicity, chorioamniotic separation, bleeding from the placenta as a result of study intervention and anhydramnios.

8.6.2 IRB Notification of SAEs and Other Unanticipated Problems

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

See Section 1.5.2 for a list of potential maternal and fetal complications to the intervention. The Investigator will promptly notify the IRB of all Unanticipated, Serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to pregnant women/fetus/children or others will also be reported promptly.

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

The sponsor-investigator will promptly review documented Unanticipated Adverse Device Effects and as necessary shall report the results of such evaluation to FDA within 10 working days and Mayo IRB within 5 working days of initial notice of the effect. Thereafter the sponsor-investigator will submit such additional reports concerning the effect as requested.

8.6.3 Sponsor-Investigator Reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unanticipated adverse device effects according to the required reporting timelines, formats and regulations.

The sponsor-investigator will submit a completed report to the FDA’s Center for Devices and Radiological Health for any observed or reported adverse effect that is determined to be an

unanticipated adverse device effect. A copy of this completed form will be provided to the DSMB and all participating sub-investigators.

The report will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation shows that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the sponsor-investigator will submit a report as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted report, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of any previous, similar report(s).

Subsequent to the initial submission of a report, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Process

The contact information for submitting reports is:

Food and Drug Administration
Center for Devices and Radiological Health Document
Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

8.6.4 Deviations from the investigational plan.

The sponsor-investigator shall notify Mayo IRB (see 21 CFR 56.108(a) (3) and (4)) of any deviation from the investigational plan 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 later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor-investigator is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB notification in accordance with 21 CFR 812.35(a) also is required.

8.6.5 Follow-up Reports

If a SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be

submitted to the IRB. The investigator will be responsible for ensuring that all SAE are followed until either resolved or stable.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report, to the investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.6.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.7 *Medical Monitoring*

It is the responsibility of the sponsor-investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safetymonitoring plan (see Section 10 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.7.1 Independent Data and Safety Monitoring Board

This study will use the currently established independent Department of Surgery Data and Safety Monitoring Board (DSMB) which meets quarterly reviewing each study at least bi-annually. Special meetings of the DSMB may be convened more often, as necessary, to address urgent concerns regarding patient safety and data integrity.

Membership of the DSMB will include those with expertise in the field, experience conducting human subjects research and statistical knowledge, independence from direct management of the study and an absence of conflict of interest.;

- The chair of the DSMB (voting member), chosen from the physician representatives
- Additional three or more physician representatives (voting members)
- Biostatistician representative (voting member)
- Representative from the Surgical Clinical Research Office (non-voting members)
- *Ad hoc* members appointed to the committee by the chair when additional expertise is required in reviewing certain studies (study-specific non-voting members)
- A quorum is defined as three or more voting members of the committee that must include at least one physician and one statistician.

Initial Review:

The DSMB may meet prior to enrollment of subjects to review the protocol, informed consent and the Data Safety Monitoring Plan (DSMP) to determine:

- The study's risks and benefits and safety of research subjects
- Suggest improving the study design
- Identify what data will be required for review
- Identify early stopping rules
  - All trials are required, when appropriate, to have early stopping rules for toxicity and for efficacy. Early stopping rules are required when an intervention of more than minimal risk is used. Efficacy is assessed in an interim analysis when such analysis can appropriately be obtained as part of the study. Design and implementation of the stopping rules are the responsibility of the study principal investigator (PI) and the study statistician. The Surgery Peer Reviewed Research Committee (SPRRC) is responsible for reviewing the proposed rules and approving them, during the standard protocol review process, for submission to the Institutional Review Board (IRB). The IRB has the final approval of the study, including the stopping rules.

Bi-annual Review:

- Interim data review to detect evidence efficacy or adverse events and determine if the study should continue, be modified or be stopped.
- Progress evaluation to assess recruitment and retention of subjects, protocol adherence, and data quality/completeness and accrual.

Meeting Timing and Frequency

The DOS DSMB meets quarterly reviewing each study at least bi-annually. Special meetings of the DSMB may be convened more often, as necessary, to address urgent concerns regarding patient safety and data integrity.

Studies identified by the IRB for more intensive monitoring may be reviewed on a quarterly, rather than semiannual basis. Special sessions of the DSMB may be held to address protocol specific issues, as necessary if the events of that protocol require review prior to the next scheduled DSMB meeting. Such meetings may occur through an electronic format.

Meeting Agenda and Format

The Principal Investigator will be notified **4** weeks prior to the scheduled meeting. The Principal Investigator will be expected to submit the required reports **2** weeks before the meeting.

DSMB members will receive an agenda with information for the studies to be reviewed approximately one week prior to DSMB meeting to allow for preliminary study and review. The information to be distributed prior to the meeting includes a listing of serious adverse events, a copy of IRB annual progress report if submitted since last DSMB review and, if available, an interim analysis.

- Each study is assigned two primary reviewers for review, presentation during the DSMB meeting and making a recommendation. The primary reviewers may ask the PI for additional information or clarification in advance of the meeting.
- If a Committee member is either a principal investigator or co-principal investigator, statistician or other study team member for a study under review, or has any other conflict of interest (including substantial financial interest in the study sponsor), that member may be present to answer questions regarding the study, but must abstain from voting and leave the room prior to final deliberations and voting on that study. If the Chair is the principal investigator for the study, another member of the Committee oversees the Committee deliberations and voting.

The meeting format may include both a Closed Session and an Open Session as required by each protocol.

Open Session:
The DSMB may request the Principal Investigator and/or study team to attend to provided clarification or respond to issues. The open session will focus on the conduct and progress of the study and review the safety and efficacy data.

Closed Session:
Only DSMB members should be present at the closed session. In this session the DSMB will review the data and evaluate the study:

- conduct (accrual),
- safety (adverse events) and
- data integrity (eligibility and protocol deviations)
- the risk benefit ratio for trial subjects

Meeting Materials
DSMB interim report templates will be prepared by the study team and the statistician, for review at the DSMB meeting. Interim data reports that summarize the safety data and describe the status of the study generally consist of two parts:

Part 1 – Open Session Report
1. Accrual summary that describes subjects screened, enrolled, completed or withdrawn.
2. A listing of adverse events and serious adverse events blinded to treatment group.
3. A copy of the annual Mayo IRB continuing review

Part 2 – Closed Session Report
This confidential report is generally the same as the open session report but unblinded to treatment group. This report may also include data on study outcomes including safety data.

Meeting Outcomes

In the closed session the DSMB will vote to take one of the following actions for each protocol reviewed and present their recommendation to the Principal Investigator:

1. **Full Approval:** enrollment may continue; no outstanding questions regarding adverse events or study progress.
2. **Conditional Approval:** enrollment may continue with the requirement for submission by the principal investigator of a satisfactory response to DSMB concerns. If the principal investigator fails to provide a satisfactory response within **14** days or receives an additional extension beyond this time period, enrollment in the study will be suspended.
3. **Suspension:** enrollment immediately suspended pending principal investigator response to DSMB concerns.
4. **Closure:** study closed due to unacceptable adverse event occurrence rate or other study issues as deemed appropriate by the DSMB.
5. The occurrence of events that prompt the activation of the protocol specific early stopping rules for pilot, phase II, and phase III studies require prompt review by the study team. The study team formulates an appropriate plan of action to ensure patient safety (as required by the FDA & IRB). This may include protocol changes and may also require immediate suspension of accrual, as deemed necessary to ensure patient safety.

The study team then forwards the action plan to the DSMB chair for review. A copy of the action plan is also provided to the DOS DMSB for review at the time it is submitted to the FDA & IRB. The DSMB provides a prompt review of the action plan and a summary of that review to the IRB and to the study team. The review by the DSMB serves as an advisory statement to the IRB and either expresses approval of the action plan or provides recommendations for modifications to the plan. The suspended study may only be re-opened after the sponsor-investigator has received FDA approval to do so. It will not be re-opened without proper protocol modification.

Minutes

- All decisions of the DOS DSMB are maintained in the minutes of the committee. The decisions of the committee are also conveyed in writing to the principal investigator of the study, the study statistician, and the IRB. If the DOS DSMB recommends immediate suspension or closure of a study, the PI and or study team will receive written notification from the DSMB chair.
    - Principal investigators may appeal the decisions of the DOS DSMB by submitting a written appeal to the chair of the DSMB. If the decision regarding the appeal is unsatisfactory to the investigator, a second appeal may be made to the Chair of Surgery Research.
- Suspension or closure of any FDA regulated clinical trial by the DSMB will be reported immediately to the FDA by the PI. If the suspension is temporary, the PI will notify the FDA & IRB of the steps taken to remedy the issues that led to the suspension.

9 Data Handling and Record Keeping

9.1 *Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 *Source Documents*

Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. When applicable, information recorded on the CRF shall match the Source Data recorded on the Source Documents.

9.3 *Case Report Forms*

A Case Report Form (CRF) will be completed for each subject enrolled into the clinical study. The investigator-sponsor will review, approve and sign/date each completed CRF; the investigator-sponsor's signature serving as attestation of the investigator-sponsor's responsibility for ensuring that all clinical and laboratory data entered on the CRF are complete, accurate and authentic.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked,

write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not obliterate, erase, or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Security and Confidentiality

Data will be entered into a secure password-protected database (REDCap) with access limited to the study team as delegated by the Principal Investigator. Study participants will be assigned an individual code at the time of enrollment which will be applied to all of their data, allowing for increased confidentiality during data analysis. REDCap allows participant data to be downloaded in a de-identified manner and also includes and audit trail for all data entry and subsequent changes to data.

9.4 *Records Retention*

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports during the study and for the longer of the following;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717,

   OR

2. A period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

10 Study Monitoring, Auditing, and Inspecting

10.1 *Study Monitoring Plan*

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

This study will use the currently established independent Department of Surgery, Data and Safety Monitoring Board (DSMB) which meets quarterly.
This study will be monitored on a routine basis during the conduct of the trial. The Mayo Clinic Office of Research Regulatory Support will provide assistance and guidance with clinical trial monitoring activities as a service for the sponsor-investigator. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects. This will assist sponsor-investigators in complying with Food and Drug Administration regulations.

10.2 *Auditing and Inspecting*

The sponsor-investigator will permit study-related monitoring, audits, and inspections by the IRB, the monitor, and government regulatory agencies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The sponsor-investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as a sponsor-investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 *Funding Source*

The fetal i*n utero* repair of spina bifida is considered part of the standard of prenatal care for those patients including the follow-up visits mentioned before. The experimental procedure

proposed in the present study is going to follow the exactly same neurological technique and same perinatal follow-up visits, which are covered regularly by medical insurances.

Therefore, the pre-surgical evaluation as well as all post-surgical visits and perinatal management will be considered part of the perinatal standard of care and the subject's insurance will be responsible for the costs associated with them. Since the *in utero* repair of spina bifida is considered part of the standard of perinatal care, verification of insurance coverage will be confirmed prior to the fetal procedure.

12.2 *Conflict of Interest*

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

13 Publication Plan

Data obtained from this study will be publicly disclosed, whether positive or negative. Whenever possible, data dissemination will occur through presentation at major scientific conferences and/or publication in peer-reviewed journals, and will be complete, accurate, balanced, and timely. The study team will not misrepresent data in these scientific communications. We will also register this study on Clinicaltrials.gov and the enrollment of patients in the present study will start only after registration.

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