Title:	Fetoscopic Spina Bifida Repair using a Cryopreserved Human Umbilical Cord Allograft (NEOX Cord 1K®) as a Meningeal Patch
Short Title:	Fetoscopic NEOX Cord 1K® SB Repair
Biological Material:	Cryopreserved Human Umbilical Cord Allograft (NEOX Cord 1K®)
Indication:	To fetoscopically use cryopreserved human umbilical cord allografts, named NEOX Cord 1K®, as a spinal cord cover of spina bifida defects. This procedure will be performed to create a watertight seal covering over the spinal cord in order to decrease the incidence rates of postnatal morbidities. Additionally, NEOX Cord 1K® may be used as a skin cover for larger defects.
FDA IDE Number:	G190253
National Clinical Trial (NCT) Number:	NCT04243889
Sponsor-Investigator:	Ramesha Papanna, M.D., M.P.H.
eIRB Number:	HSC-MS-19-1051
Protocol Date:	06/21/2024

Sponsor and Study Principal Investigator:

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[redacted]

Version Number: 4.0

CLINICAL TRIAL PROTOCOL

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IRB NUMBER: HSC-MS-19-1051
IRB APPROVAL DATE: 09/26/2024

Summary of Changes from Previous Version:

Affected Sections	Summary of Revisions	Rationale
1.1 Under synopsis	"Data collection" was added	Data collection was included to clarify that at the hospital time point, it is not a study visit and the 1 month timepoint the patient may still be in the hospital and data would be collected
1.2 Under Schema	"Data collection" was added	Data collection was included to clarify that at the hospital time point, it is not a study visit
5.5 Under Strategies for Recruitment and Retention	Language was added about follow-up visits.	If follow-up visits are not covered by insurance, the research study will pay for the visits.
8.1.4 Title	"Data collection" was added	Data collection was included to clarify that at the hospital time point it is not a study visit
8.3.1under Definition: Adverse Event (AE)	The following was added "An adverse event is any undesirable or unintended effect of the research occurring in human subjects as a result of the research or the collection of private health information under the research."	Clarifying the definition of adverse events
8.3.1under Definition: Adverse Event (AE)	The severity definitions were deleted.	AEs will be reported as serious or non-serious and not include the type of severity.
8.3.4 Expectedness	Removal of unrelated unanticipated problems	If this language is kept in the protocol, there will be an overreporting of events that do not need to be reviewed by the FDA or IRB.
8.3.4 Expectedness	Specified unanticipated	Expectedness was revised to specify unanticipated adverse

	adverse device effects	device effects.
8.3.5 under IRB Notification of SAEs and Other Unanticipated Problems	Removal of reporting adverse events whether or not related to the trial was removed	If this language is kept in the protocol, there will be an overreporting of events that do not need to be reviewed by the FDA or IRB.
8.3.12- A new section was added, Recording of Developmental Milestones	A new section was added "The primary outcome objective of this study is ambulation at 30 months. To properly assess ambulation, the study team will ask parents/guardians to send video recordings of changes to their child's mobility. Communication sent to the research team with images and videos of ambulation and different milestones will be used for future research exploratory analysis. Additionally, research staff will take a video recording of the child walking or mobilizing at the 12 month, 30 month, and 60 month visit time points."	We would like to collect videos of the primary outcomes

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

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

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1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Study Title Early Feasibility Study of Fetoscopic Spina Bifida Repair using a Cryopreserved Human Umbilical Cord Allograft (NEOX Cord 1K®) as a Meningeal Patch

Funder University of Texas McGovern Medical School's departmental funds

Clinical Study Early Feasibility Study

Primary Objectives To test the feasibility of surgically covering spina bifida spinal cord developmental defects as a meningeal layer using cryopreserved human umbilical cords (NEOX Cord 1K®) via a laparotomy-fetoscopic surgical approach. For larger skin defects, NEOX Cord 1K® may be used as a skin cover. The primary outcome is successful surgical closure of the defect, and the secondary outcomes are the rate of repair dehiscence and/or leakage of cerebrospinal fluid at birth and at 12 months of age.

Investigational Devices The following investigational devices will be evaluated in this study:-

- Cryopreserved human umbilical cord allografts (NEOX Cord 1K®; homologous use of a 361 HCT/P biological material), Tissue Tech., Inc.;



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Study Design

This is an open label, non-randomized, single arm, prospective clinical trial of 50 patients with a spina bifida defect. Patients intending to undergo open *in-utero* spina bifida repair, will be offered to be screened for an alternative minimally invasive approach. All eligible pregnant mothers' fetuses within the trial will receive NEOX Cord 1K® as a spinal cord cover to close the developmental defect. In some cases, at the discretion of the Neurosurgeon, NEOX Cord 1K® may be required to cover the skin. All eligible subjects meeting all inclusion criteria but none of the exclusion criteria may be enrolled. Please see inclusion and exclusion criteria below.

Briefly, under general anesthesia and tocolysis, *in-utero* repair begins with a laparotomy that is followed by exteriorization of the uterus. The fetus is then positioned by external cephalic version. Uterine entry will be accessed using 3 cannulas, followed by heated-humidified carbon dioxide insufflation for visualization. Then, fetoscopically the placode will be examined and dissected. The lesion will be repaired using NEOX Cord 1K® (HUC), under Right of Reference for 361 HCT/P designation, for the closure of the first layer over the neural placode (Fig. 1). Primary closure of the skin (Fig. 1A) will then occur, or NEOX Cord 1K® (HUC) will be used for skin closure (Fig. 1B) at the discretion of the neurosurgeon. Finally, the laparotomy site will be sutured in multiple layers.

[redacted]

If the mother does not show preterm labor, the mother may undergo vaginal delivery at term except if there's an obstetrical indication for a cesarean section delivery.

Subject Population

Maternal Inclusion Criteria

1. Singleton pregnancy
2. Gestational age at screening is 19 to 25^5 weeks and gestational age at surgery is 22 to 25^6 weeks
3. Maternal age: 18 years and older
4. Body mass index <40 kg/m^2
5. No preterm birth risk factors (short cervix, history of previous preterm delivery)
6. No previous uterine incision in the active uterine segment
7. Willing to undergo an open fetal repair if the fetoscopic approach is unsuccessful

Fetal Inclusion Criteria

1. Spina bifida defect between T1 to S1 vertebral levels
2. Chiari II malformation
3. No evidence of kyphosis (curved spine)
4. No major life-threatening fetal anomaly unrelated to spina bifida
5. Normal karyotype, or normal CMA, or a CMA with variants of unknown significance.

Maternal Exclusion Criteria

1. Non-resident of the United States
2. Multifetal pregnancy
3. Poorly controlled insulin-dependent pregestational diabetes
4. Poorly controlled A2DM insulin-dependent diabetes
5. Current or planned cerclage or documented history of an incompetent cervix

6. Placenta previa or placental abruption
7. Short cervix of < 20 mm
8. Obesity as defined by a body mass index of > 40
9. Previous spontaneous singleton delivery prior to 37 weeks
10. Maternal-fetal Rh isoimmunization, Kell sensitization, or a history of neonatal alloimmune thrombocytopenia
11. HIV or Hepatitis-B positive status
12. Known Hepatitis-C positivity
13. Uterine anomaly such as large or multiple fibroids or a mullerian duct abnormality that is diagnosed via imaging prior to surgery, which that are unavoidable during surgery
14. Other medical conditions which are contraindication to surgery or general anesthesia
15. Patient does not have a support person
16. Inability to comply with the travel and follow-up requirements of the trial
17. Patient does not meet psychosocial standardized assessment criteria
18. Participation in this or another intervention study that influences maternal and fetal morbidity and mortality
19. Maternal hypertension
20. Zika virus positivity
21. Allergy/history of drug reaction to Amphotericin B

Fetal exclusion criteria

1. Major fetal anomaly not related to spina bifida
2. Kyphosis in the fetus of 30 degrees or more
3. Ventriculomegaly greater than 15 mm and no movements noted at hip and knee joints

Number of Subjects Initial enrollment: 50 subjects

Study Sites Single center investigational site: University of Texas Health Science Center at Houston/TFC at Children's Memorial Hermann Hospital.

Study Duration Based on an estimate of one enrolled subject per month, the recruitment phase of the study is estimated to be ~50 months. All children will be followed and monitored throughout their 60-66 month follow-up visit. Therefore, the entire duration of the study is estimated to be ~10.5 years.

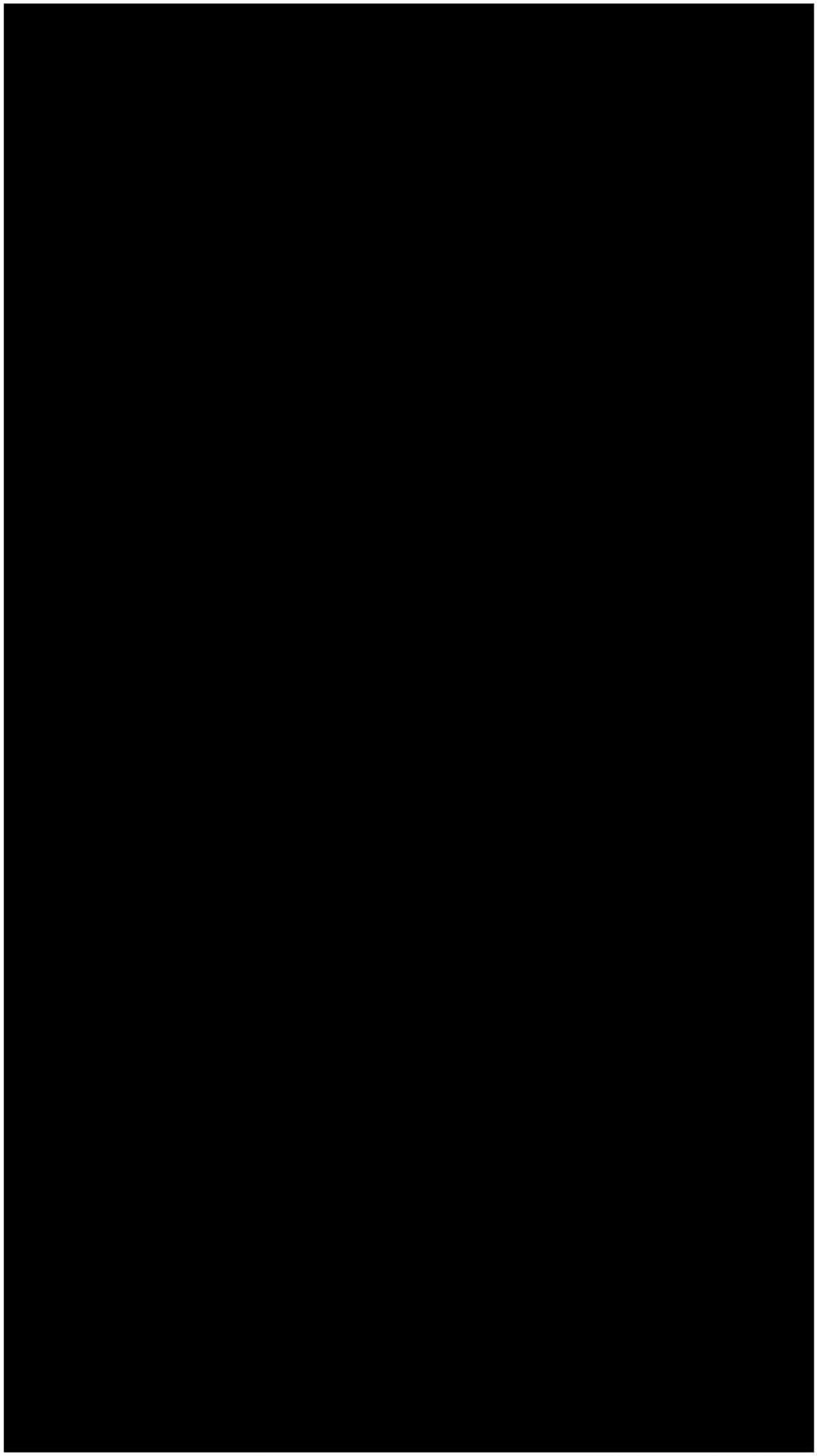
Study Phases

Screening Eligibility screening and to obtain consent.

Study Device Intervention: Cryopreserved human umbilical cord allografts (NEOX Cord 1K®) will be used to cover the spinal cord prior to skin closure, that is primary skin closure or through the use of NEOX Cord 1K®, via a fetoscopic procedural approach.

Follow-up Visits/ data collection NICU / inpatient, 1 month, 12 months, 30 months, and 60 months.

Efficacy Evaluations All subjects will be followed for a total of 60-66 months from birth to



[redacted]

Safety Evaluations

Adverse events, serious adverse events, procedural complications, and neonatal outcomes will be monitored and reported.

Statistics

Summary statistics and frequency tables will be used in this early feasibility study for the determination of safety and feasibility of performing fetoscopy to repair of spina bifida defects using NEOX Cord 1K® as a meningeal or dual meningeal and skin patch at our institution.

Data and Safety Monitoring Plan

To ensure subject safety, an independent Data and Safety Monitoring Committee (DSMC) will be assembled at the University of Texas Health Science Center at Houston, to include a statistician, the McGovern Chair in Medical Humanities, a Pediatric Neurosurgeon, and a medical monitor. The study's Sponsor-Investigator or designee will report case outcomes after delivery and after the neonate's first 30 days of life to the DSMC at scheduled semi-annual meetings, or at the discretion of the DSMC. The DSMC will convene to evaluate the study's results once 3 neonatal patients have been alive for 30 days, or alternately after a year from when the study was initiated; whichever comes first. In addition, the DSMC will convene semi-annually to ensure subject safety. The DSMC will be contacted if there are any safety concerns that arise during the study. Following the initial review of the protocol, subsequent DSMC meetings will be

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assembled at their discretion, however, the occurrence of a semi-annual meeting will be mandatory.

1.2 SCHEMA

Please see Figure 2 for a process diagram of the study's overall schema.

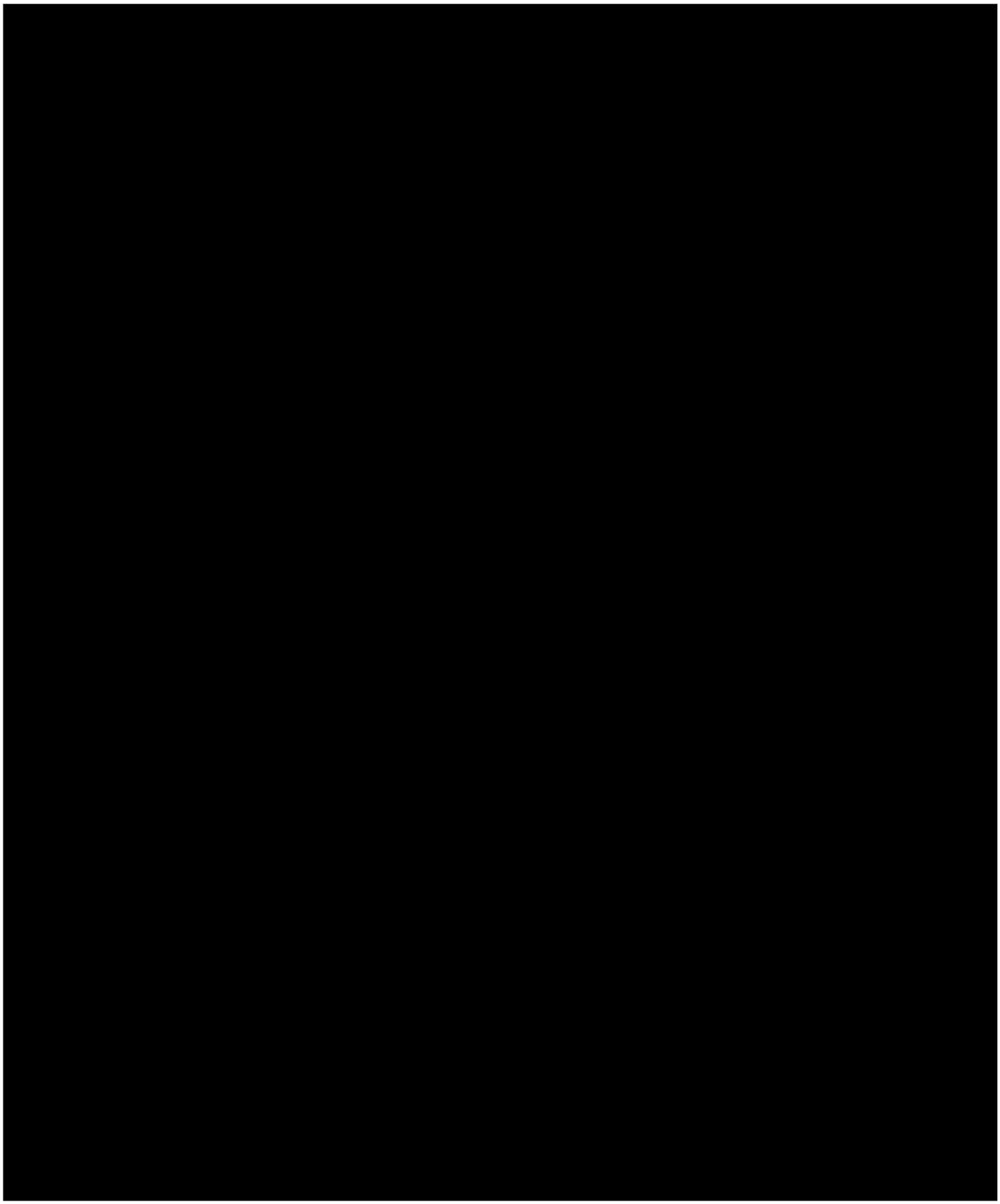
Screening

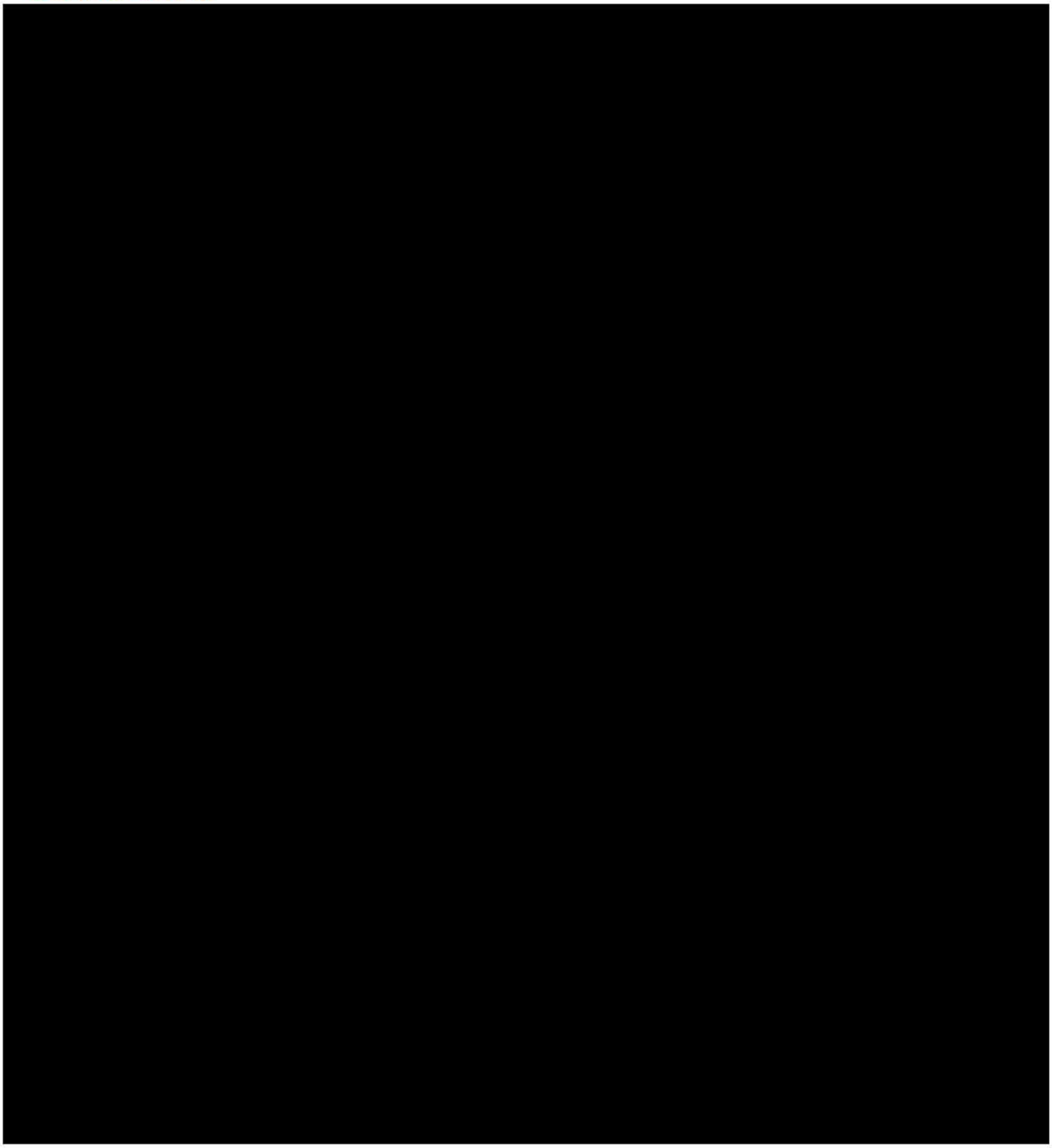
- Mother and fetus will be screened by inclusion and exclusion criteria
- Obtain informed consent
- Obtain history and current medications and / therapies
- Surgery clearance by an anesthesiologist and by obstetrics staff
- Provide patients with instructions on SOC medications
- Schedule the fetoscopic repair surgery at gestational age 22-25^{6} weeks

Fetoscopic *In-utero* Repair (please see Figure 3 for an overview of the study's intervention procedure versus SOC).

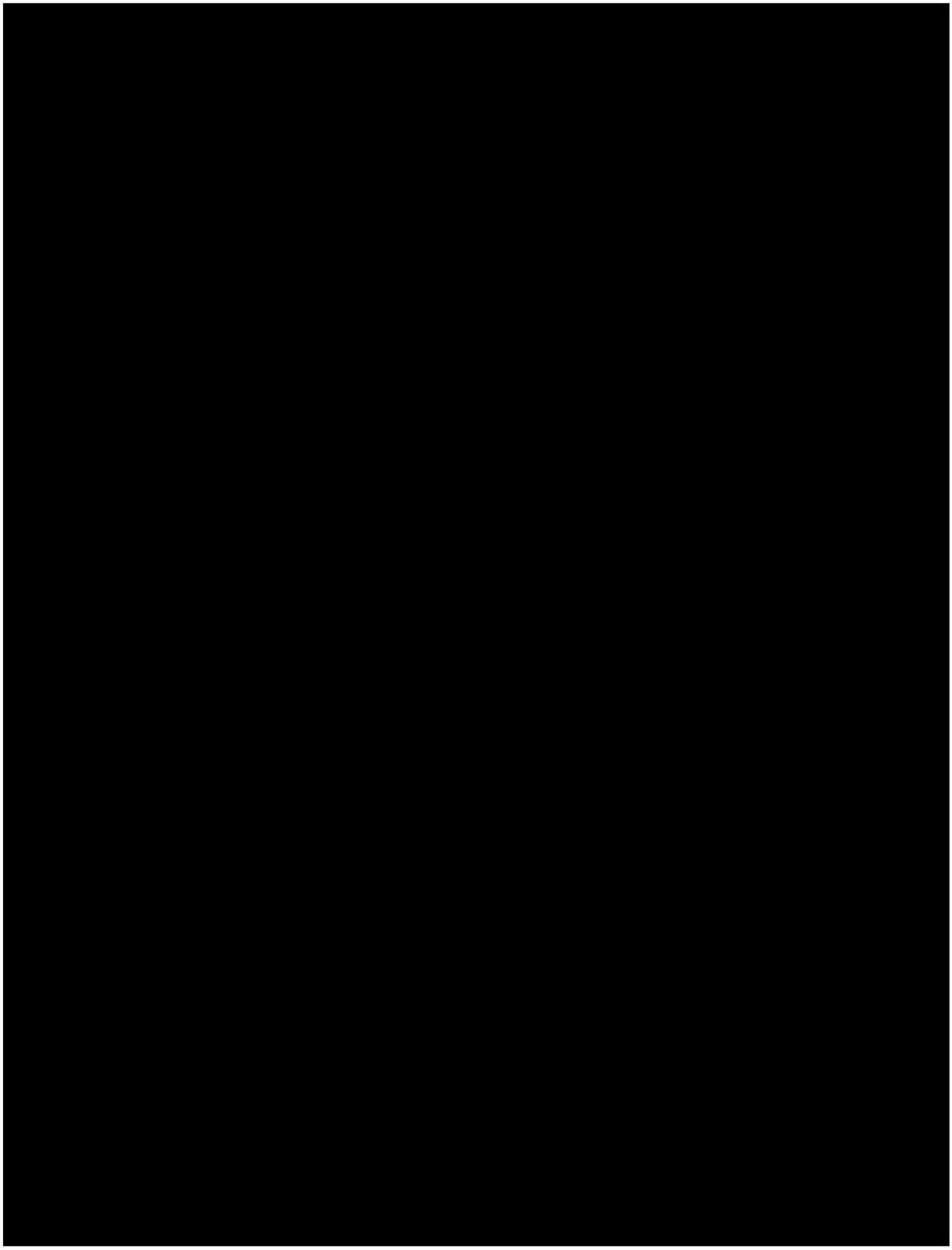
- Perform the fetoscopic surgical procedure with the use of NEOX Cord 1K®
- Document the repair through repair capture throughout the surgical case (pre-repair, following placode dissection, following spinal cord covering with the sutured NEOX Cord 1K® patch, and primary skin closure or skin closure using NEOX Cord 1K®)
- Post-surgical recovery closely monitored

[redacted]









2. INTRODUCTION

2.1 BACKGROUND

Diagnosis and Prognosis of Spina Bifida

Spina bifida is estimated to affect 3.5 fetuses per 10,000 live births in the United States of America (USA) [2]. Spina bifida occurs during early embryonic development when a neural tube fusion defect results in incomplete closure of the spinal vertebrate column around the spinal cord. The overarching disease is subdivided into spina bifida occulta and spina bifida cystica. The former occurs when there is a hidden split in the vertebrae, and the latter when there is an open neural tube defect resulting in a cyst-like protruding mass. A meningocele occurs if the protruding mass does not contain a portion of the spinal cord, whereas the most common type of spina bifida, a myelomeningocele, is resultant from the protruding mass containing a portion of the spinal cord that is protected by the meninges. If the spinal cord protrudes as a mass without an overlying membrane, then it is known as myeloschisis, which is the most severe form of spina bifida.

Spina bifida is associated with a wide spectrum of clinical manifestations. Presentation includes HH, an array of neurological deficits, bowel and urinary dysfunction, and hydrocephalus. The total lifetime medical costs associated with treatment of spina bifida is estimated to be $340,000 per patient (adjustment for inflation) [3], accounting for an approximate $500 million per annum economic burden to the US. [4, 5]

Spina bifida is often diagnosed *in-utero* in the second semester by ultrasonography and by screening maternal serum for alpha-fetoprotein. For decades the standard of care has been to perform post-natal repair of the open neural tube defect so as to prevent additional degradation of the child's spinal cord (Figure 4).

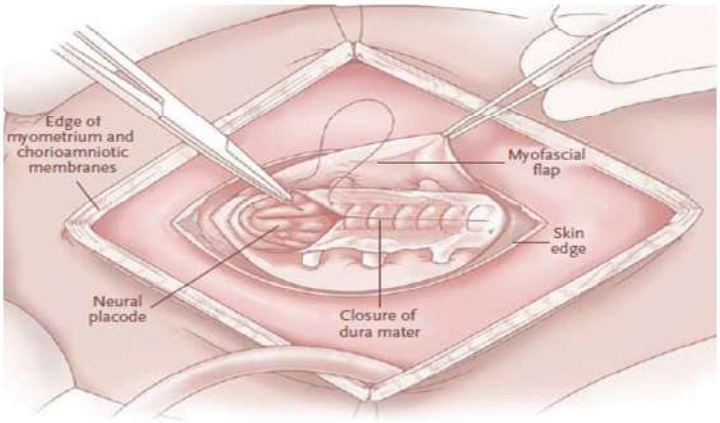


Figure 4. Primary repair of a myelomeningocele *in-utero* with a multilayer primary repair without the use of a patch. Adapted from chop.edu.

The survival rate for patients that did not receive standard of care surgery is estimated to be 20% within the first two years of life.[6] Amongst the most frequent abnormalities associated with spina bifida are Chiari malformation (CM) and hydrocephalus. The Chiari type II malformation is the most common, which is characterized by cerebellar vermis caudal descent that displaces the fourth ventricle and lower brain stem. HH has been postulated to occur as a result of ventricular cerebrospinal fluid (CSF) leakage through the open defect. Obstructive hydrocephalus develops when the fourth ventricle becomes occluded from the impact of brain tissue. About 15- 25% of children with spina bifida will have hydrocephalus at birth, at which point a shunt is placed postnatally to alleviate pressure in the blocked ventricle and excess CSF is drained into the peritoneum. Approximately 17% of these cases will have CSF leakage for 5-6 days after their postnatal defect closures [7-9], and leakage reparation carries with it an inherent 1-12% risk of infection. [10, 11] Even if the CSF leakage is repaired, 80% of the patients develop hydrocephalus within two weeks of birth as a result of increased cerebral ventricle pressure.[12, 13] Ultimately within the first year of all patients' lives, 96% will develop HH and 72% will have an abnormal location of the fourth ventricle [1, 14] leading to an 86-98% requirement for a CSF shunt placement. [1, 14, 15] Shunt malfunctions and infection rates are a frequent occurrence in the first postoperative year, and 95% of patients will have shunt-associated problems within 20 years [16, 17].

Typically only 21% of patients will be able to walk within the first 30 months from birth [1], and dependent on the vertebral section and vertebral level of the initial lesion, ambulatory capabilities range between 0% and 93% in 20-25 year old patients.[17] Additionally, the most common skeletal deformity is clubfoot and has been reported in 30-50% of patients at birth. [1, 18-21]

Another source of significant morbidity and mortality for those with spina bifida is urological complications, even if the patient is ambulatory. Due to dysfunctions of the somatic, parasympathetic, and sympathetic systems, poor bladder dynamics may ultimately cause chronic kidney disease.[22] As a result of hydronephrosis, more than 50% of patients require clean intermittent catheterization (CIC) to control urination within the first 30 months of life, and approximately 85% of patients will need CIC by 10 years old.[23, 24] Since approximately 85% of patients have urinary incontinence, many of these patients would require major urological surgery within the first 10 years of life.[24]

If spinal tethering is left untreated, neurological damage may occur as the child grows. To prevent further neurological deterioration, patients that develop symptomatic tethering of the spinal cord by age 20 would require surgical intervention.[17, 25, 26]

It has been estimated that the 5 year mortality rate of those with spina bifida is 34% [27], with an increased survival rate of 76% between the ages of 20-25.[17] Of the patients that survive, between 30-37% are able to live independently as adults having intelligent quotients of 80 and above.[28]

In-utero repair reduces clinical morbidity and mortality rates

Due to *in-utero* exposure of the spina bifida fetus to amniotic fluid, hence to meconium and urea, along with the mechanical trauma during fetal movements and contractions, increasing damage to the open spinal cord occurs.[29] In order to mitigate spinal cord damage, the first *in-utero* repair of spina bifida defects via hysterotomies were performed in 1997.[15, 30] Since the results of the aforementioned early studies were promising, outcomes of *in-utero* versus postnatal spina bifida defect repair were investigated in a multicenter, NIH-supported, randomized prospective trial named the Management of Myelomeningocele Study (MOMS). Three fetal surgery centers participated in the MOMS trial, namely the Children's Hospital of Philadelphia, Vanderbilt University, and the University of California at San Francisco. This pivotal trial led to *in-utero* repair becoming the standard of care in most cases. The MOMS trial showed that HH decreased by 32% at 12 months in the *in-utero* repair cases when compared to the postnatal closure cases. This result is most likely due to the reduction / elimination of CSF leakage from closure of the defect *in-utero*. It is interesting to note that an unknown reason for delayed onset HH may occur in up to 36% of children at 6 months old, which almost doubles by a year of age. Even though the percentages of HH in postnatal *in-utero* repaired spina bifida cases are reasonably high, approximately 96% of patients repaired in the postnatal population will present with HH within 12 months.[1] Due to these statistics and others, the standard of care has become *in-utero* repair for the majority of cases.

Arnold-Chiari malformation is resultant from a structural defect in the cerebellum. This may lead to non-communicating hydrocephalus as a result of CSF outflow obstruction, leading to the subsequent need for shunt placement surgery. It has been reported that in one year old patients whom underwent *in-utero* defect repair that 54% of the population had a more normal anatomic location of the hindbrain and hence the fourth ventricle as opposed to 28% of patients who had their defects repaired postnatally.[1] Approximately 40-59% of *in-utero* repair patients versus 82-91% of the postnatal repair group received shunt placement surgery.[1, 14, 31, 32]

Notwithstanding the good results obtained in HH prevention in the *in-utero* repair patients, there are conflicting results on sensorimotor function benefits.[33] Numerous reports have suggested no improvement in leg motor skills between the two groups, however it has also been suggested that leg function can be correlated with the level of the lesion.[13, 31, 34, 35] The MOMS trial reported that 42% versus 21% of patients with *in-utero* or postnatal repair, respectively, were able to walk independently. *In-utero* patients had overall better motor function skills, which were assessed by a number of standard motor skill function tests. Notably, club-foot deformity and higher lesion levels lowered the likelihood of being able to walk independently in the fetal intervention group when compared to postnatal historical controls. However additional data requires capturing and analysis post two years from birth.[1, 14, 36]

At birth over 90% of children born with spina bifida will have normal upper urinary tracts, however over time 50% of the population will suffer renal deteriorization. Medical management may aide in suppressing the deleterious effects of incontinence, however surgical intervention will most likely be required. No differences in urinary function has been noted in patients who have undergone prenatal versus postnatal defect repair in 2-26 year olds.[23, 24, 37, 38]

There is a high prevalence of no visible scarring associated with *in-utero* repair patients, leading to the postulation that fetal repair leads to improved wound healing and a resultant reduction in tethered cord rates, it has been unfortunately documented that tethered cord surgery will be required in 8% of the population by age one [1], and at a similar rate by ages 7-9, compared to 1% of postnatal repair patients.[24, 37] A definitive cause for tethering of the spinal cord needs to be established, and additional studies are required following *in-utero* repair.

Additionally, 44-46% of all various fetal surgery cases deliver preterm at less than 34 weeks when compared to 5% of the general population.[1, 39] No statistical differences have been found in mortality rates of all fetal surgery cases versus the postnatal surgery population [1, 31, 32, 40], however this has not yet been assessed for long-term cases involving spina bifida fetal repair cases.

Complications Arising Postnatally Despite In-utero Surgical Repair

Table 2 provides an overview of postnatal risk factors associated with prenatal versus neonatal spina bifida repair. The data from Table 2 was extracted from Adzick *et al*, 2011.

Table 2. Postnatal complications of *in-utero* versus neonatal spina bifida defect repair.

Significant Risk Factor	**Maternal (%)**	**Maternal (%)**
	***In-utero* Surgery**	**Postnatal Surgery**
chorioamniotic separation	36	0
pulmonary edema	6	0
oligohydramnios	21	4
placental abruption	6	0
spontaneous rupture of membranes	46	8
spontaneous labor	38	14
blood transfusion at delivery	9	1
hysterotomy scar partially or completely dehisced	35	0
subsequent pregnancy cesarean section	100	ND
Significant Risk Factor	**Neonate (%)**	**Neonate (%)**
	***In-utero* Surgery**	**Postnatal Surgery**
prematurity <30 weeks	13	0
prematurity ≤34 weeks	46	5
apnea[1]	36	22
respiratory distress syndrome	21	6
spinal cord tethering by 12 months	8	1
epidermal cysts by 12 months[1]	3	2

ND = not determined

[1] = not statistically different

As is shown in Table 2, it is of utmost importance to further improve upon *in-utero* repair surgeries for those with spina bifida given the patients' better overall prognoses compared with postnatal repair. Therefore there's an unmet need to facilitate the meticulous watertight closure of the dura, fascia, subcutaneous tissues, and the skin, primarily due to complications in approximating the skin and the fragility of fetal skin edges *in-utero*.

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2.2 STUDY RATIONALE

Fetoscopic spina bifida repair

In 2003 a randomized, multi-center, controlled trial (Management of Myelomeningocele Study, MOMS) was initiated in the USA under support from the NIH to assess the benefits of *in-utero* open surgery compared to postnatal surgery for the treatment of spina bifida. This clinical study demonstrated conclusively that *in-utero* primary repair of the defect improves the 12- and 30-month outcomes of spina bifida patients with a reduction in HH and the need for shunting. Additionally, there was a significant improvement in functional neurological outcomes, including the ability to walk without orthotics. As a result, the *in-utero* repair of spina bifida is now considered the SOC for the treatment of eligible fetuses for this rare and serious disease. The open surgery obligates c-section delivery to reduce the risk of uterine rupture. This increases the maternal risk for major surgery in the pregnancy. Also, more recent data shows that subsequent pregnancy has 9% risk of uterine rupture and associated perinatal death. The management of subsequent pregnancies would require repeat c-sections.

The fetoscopic repair of spina bifida has been offered to improve the chance of vaginal delivery to the mother, and has shown to result in longer gestation. The short-term outcomes including perinatal survival, birth weight, hindbrain reversal at birth, shunt rates by 12 months of age, appear to have similar outcomes as with open repair. However, the long term outcomes of the children remains unknown or is limited



Use of heated-humidified carbon dioxide (CO_2) gas versus use of cold-dry CO_2 gas during fetoscopic spina bifida repair

Challenges of fetoscopic surgery include the fluid-filled intrauterine environment, which

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hinders fetal visualization and immobilization in addition to surgical tool maneuverability. To overcome these barriers partial drainage of amniotic fluid followed by uterine CO_2 insufflation has been proposed. Reasons for employing the use of CO_2 for amniotic cavity insufflation includes improved visualization, its anti-combustive properties, that it's highly diffusible in the blood, is inert if leaked into the atmosphere, is inexpensive and readily available, and that it prevents the consequences of air embolisms [41].

In early studies a strong correlation was suggested between oxygen (0_2) and CO_2 exchange rates across neonatal infant skin with gestational age at delivery [42]. They determined that neonates delivered prior to 31 weeks had 6 times higher O_2 and CO_2 exchange rates across their skin compared with babies delivered at term. This suggested that fetal skin would exchange CO_2 and O_2 rapidly.

Later, several independent groups used pregnant sheep model systems to perform intrauterine endoscopy procedures in order to mitigate open fetal repair complications. However, safety concerns about partial amniotic CO_2 insufflation (PACI) came to the forefront in these studies where severe fetal hypercapnia and severe acidosis occurred during the procedures [43-46]. Studies were performed in sheep models to offset the former finding through maternal hyperventilation, however there was no consensus on optimal rates and durations thereof [45, 46].

From those studies we now know that dry-cold CO_2 insufflation pressures decrease in animal studies when performing open laparotomy procedures as opposed to fetoscopic procedures. This is summarized below in Table 3.

Table 3. Open laparotomy spina bifida defect repair is associated with decreased insufflation pressures.

	Luks, 1994 [43]	Pelletier, 1995 [44]	Saiki, 1997 [45]	Gratacos, 2001 [46]
Uterus exteriorized	Yes	No	No	Yes
Insufflation pressure (mmHg)	3-4	15	10	4-5

[redacted]

[redacted]

Later, a team of researchers examined the neurological outcomes of sheep exposed in mid-gestation to 7-15 mmHg CO_2 insufflation pressures for between 45-80 minutes, and found no neurological abnormalities when the sheep delivered spontaneously at term. Lamb brains were examined for hemorrhages, embolism, infarctions, and for any inflammatory alterations and for abnormal maturation of the cortex. They concluded that the use of PACI in fetoscopic interventions seemed safe for appropriate brain development and that maternal and fetal complications were not observed [47].

Given that prenatal MMC repair via a hysterotomy is highly beneficial [1], a progressing interest in optimization of fetoscopic intervention has been realized globally by Maternal-Fetal Medicine specialists. By performing fetoscopic laparoscopy procedures, maternal morbidities associated with hysterotomies would be circumvented and reduced rates of premature delivery would be attained. However, in early cases of fetoscopic MMC repair, high rates of preterm birth, preterm premature rupture of membranes (PPROM), maternal/fetal complications, and prenatal death when compared to open fetal surgery [48-50].

Recent studies in an ovine model found that heat-humidified PACI partially mitigates the effects of cold-dry PACI [51]. They showed that fetuses undergoing heat-humidified PACI, versus cold-dry PACI, had significantly lower arterial partial pressures of CO_2, reduced lactate concentrations, and had higher pHs [51].

In humans, when comparing fetal outcomes associated with use of cold-dry versus heat-humidified PACI, a reduced PPROM rate was noted for Belfort *et al*. (2017) and can be seen in Table 4.

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Table 4. PPROM rates when comparing heat-humidified PACI to cold-dry PACI versus open and percutaneous spina bifida repair.

	Kohl (2014) [52]	Pedreira (2016) [49]	Belfort (2017) [53]	Ziemann (2018) [54]	Lapa Pedreira (2018) [55]
n	51	10	28	65	47
Method	Percutaneous	Percutaneous	Open	Percutaneous	Percutaneous
Insufflation Pressure (mmHg)	9-30, mean 15.6	Not reported	12 ± 2	7-30, mean 12.4	10-18, mean 14
Heat-humidified PACI?	No	No	Yes	No	No
Fetal surveillance	Doppler US Fetal heart rate Fetal contractility Before/after anesthesia induction Before intra-amniotic access After amnioreduction Before CO2 insufflation At end of procedure	Doppler US Fetal heart rate Fetal contractility Before/after anesthesia induction Before intra-amniotic access After amnioreduction Before CO2 insufflation At end of procedure	Near continuous fetal-echo	Intermittent fetal Doppler	Fetal heart rate monitoring
PPROM	84.3% (43/51)	100% (10/10)	23% (5/22)	Not reported	80% (36/47)
Adverse outcomes of PACI?	No	No	No	No	No

However, in recent clinical report series of fetuses undergoing fetoscopic MMC repair using PACI more promising results have been documented, providing evidence that fetal hypercapnia in humans weren't as deleterious as was described in animal models. This may be attributable to largely avascular fetal membranes of humans versus highly vascularized sheep fetal membranes. In a human case series documenting differences in acidosis in fetuses repaired either in cold-dry PACI conditions or in heated-humidified PACI conditions, the lowest pH reduction was reported in a fetus that was exposed to heated-humidified PACI [56]. This has been postulated that this occurs due to lower CO_2 solubility at high temperatures together with reduced CO_2 partial pressures as a result of higher water vapor pressures [57].

Importantly, Sanz Cortez *et al*. (UOG, 2018) reported that no significant differences in micro- or macrostructural brain abnormalities were noted in fetuses and infants that underwent fetoscopic versus open neural tube defect repair utilizing CO_2 PACI procedures.

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Laparotomy followed by fetoscopy for spina bifida repair

Short-term outcomes of fetoscopic repair are comparable to the historical controls of the open repairs performed in the MOMS clinical trial. Of note, when a laparotomy-fetoscopic approach is used, fetuses have a longer gestation with a greater chance of being delivered vaginally. Additionally, shunt rates at a year of age are comparable when comparing outcomes from open and fetoscopic procedures. Other researchers have determined that the functional levels versus anatomic levels are also comparable to the MOMS trial by means of review of the literature.[58] However ambulation at 30 months and long-term cognitive development remains unknown.

Table 5. Summary of fetoscopic versus open spina bifida repair.

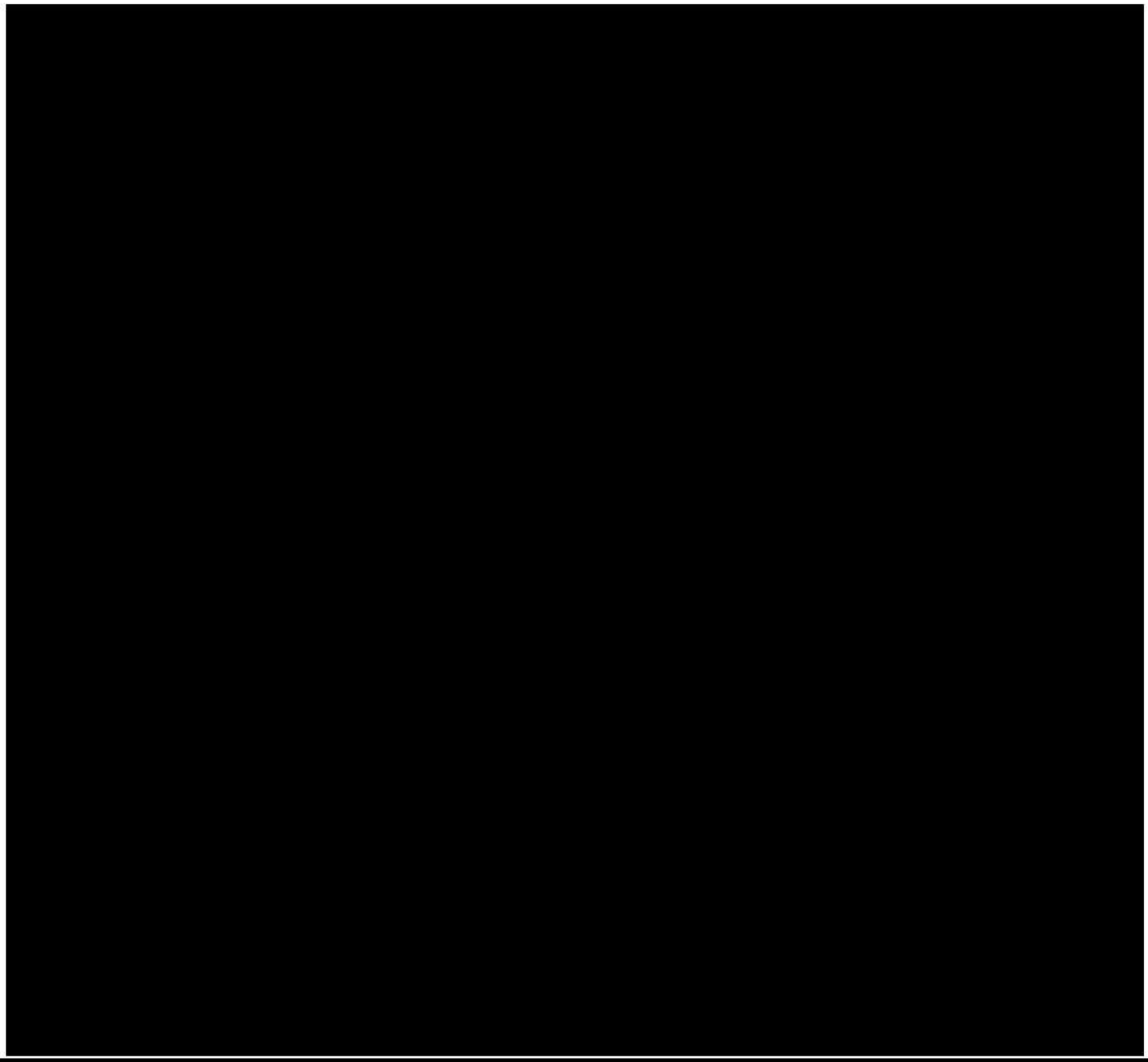
	Belfort *et al.*	Verbeek *et al.*	Pedreira *et al.*	Kohl *et al.* Degenhardt *et al.*	Graf *et al.*	Adzick *et al.* (MOMS)
Approach	fetoscopic laparotomy	fetoscopic percutaneous	fetoscopic percutaneous	fetoscopic percutaneous	fetoscopic percutaneous	open
Patients, n	28	19	10	51	71	78
Operative outcomes						
Mean operation time, minutes	250 ± 163.5	n.s.	242 ± 89	223 ± 40[b]	n.s.	105.2 ± 21.8
Intraoperative incomplete closure	21% (6/28)	15.8% (3/19)	20% (2/10)[c]	1.9% (1/51)	n.s.	0% (0/78)
Maternal outcomes						
PPROM	23% (5/22)	85% (11/13)	100% (10/10)	84.3% (43/51)	n.s.	46.2% (36/78)
Mean GA at PPROM, weeks	33 ± 3.0	n.s.	30.2 ± 2.7	29.7 ± 3.1[d]	n.s.	n.s.
Uterine thinning or dehiscence	0% (0/28)	n.s.	0% (0/10)	0% (0/51)	n.s.	35.5% (27/76)
Vaginal delivery	50% (14/28)	n.s.	8% (4/45)	n.s.	n.s.	0% (0/78)
Fetal, neonatal, and infant outcomes						
GA at delivery	38.5 ±1.2	32	32.8 ± 1.9	32.9 ± 2.7	32	34.1 ± 3.1
Preterm birth <30 weeks	0% (0/28)	n.s.	11.1% (1/9)	11.8% (6/51)	12.7% (9/71)	12.8% (10/78)
Complete reversal of CM at 1 year	57% (16/28)	n.s.	85.7% (6/7)	n.s.	n.s.	35.7% (25/70)
Shunt rate at 1 year	25% (7/28)	30.8% (4/13)	42.8% (3/7)	n.s.	45% (32/71)	40.3% (31/77)

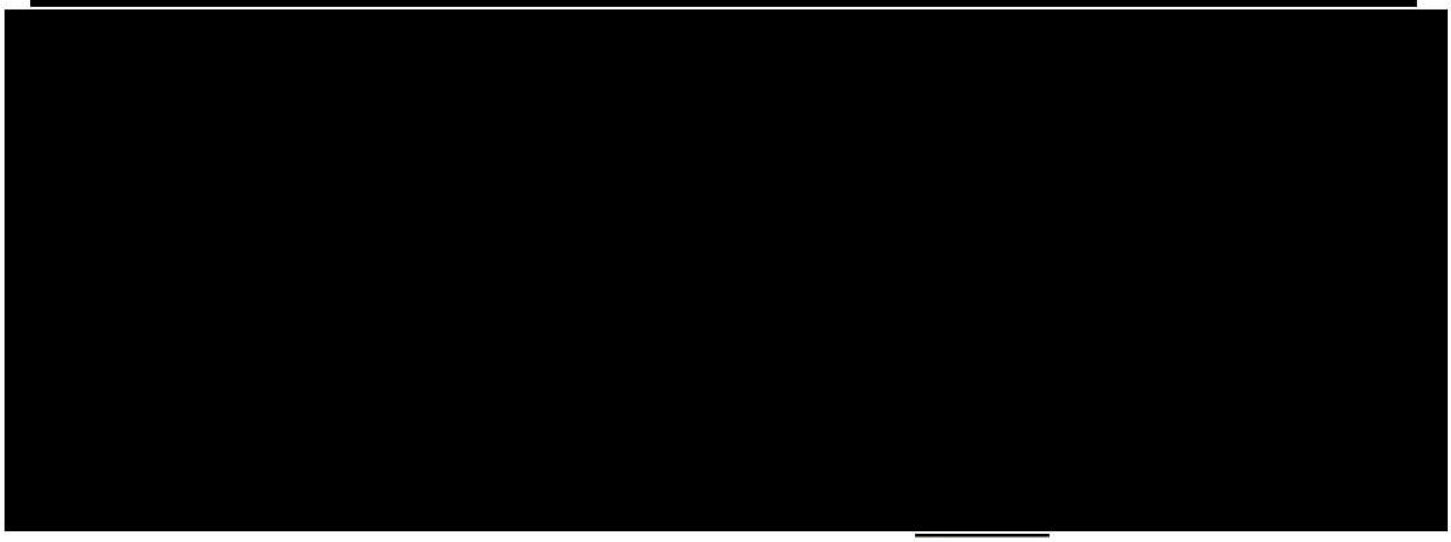
[A]Based on the number of live births
[b]Degree of CM is a mandatory inclusion criteria for all fetal surgery. It is assessed pre- and post-natally by US and / or MRI.
[c]Surgery could not be completed in 2 cases due to trocar dislodgement and CO_2 leakage into the maternal abdomen.
[d]Data from both reports are discrepant, results are based on Degenhardt *et al.*, 2014.
n.s. = not specified; PPROM = preterm premature rupture of membranes; GA = Gestational age

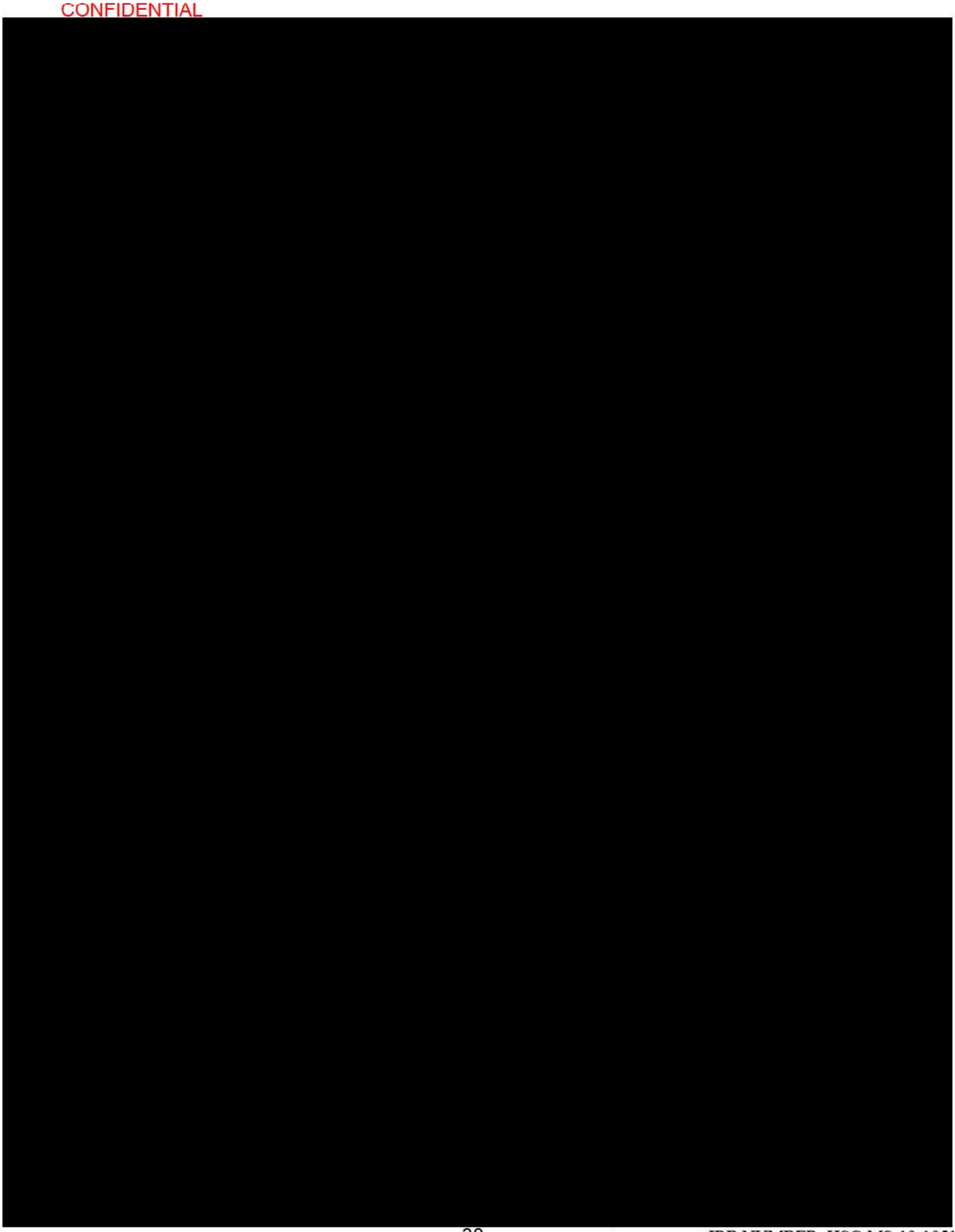
Modified from Table 2 in Joyeux *et al.*, 2015, and data extracted from Belfort *et al.*, 2017.

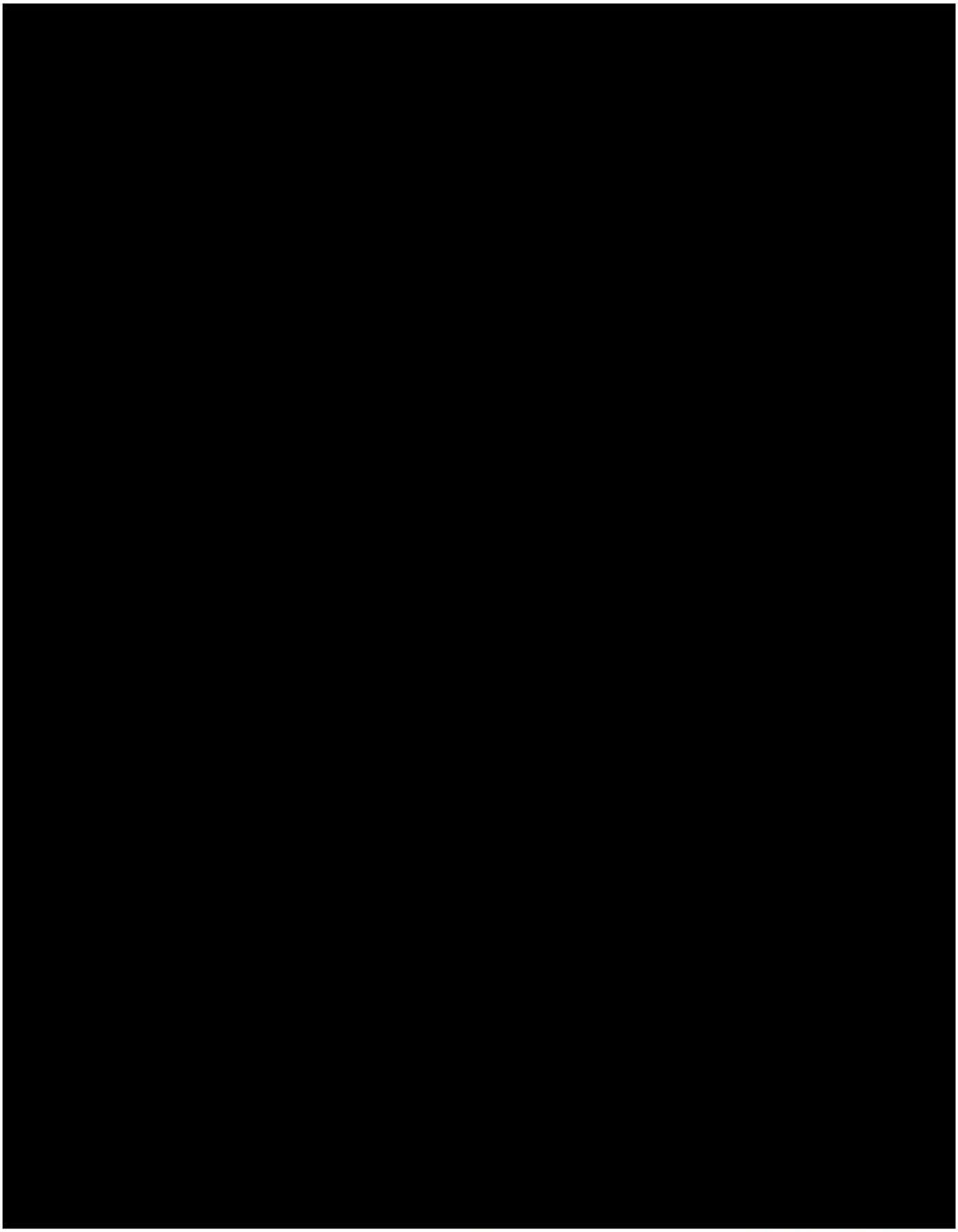
[redacted]

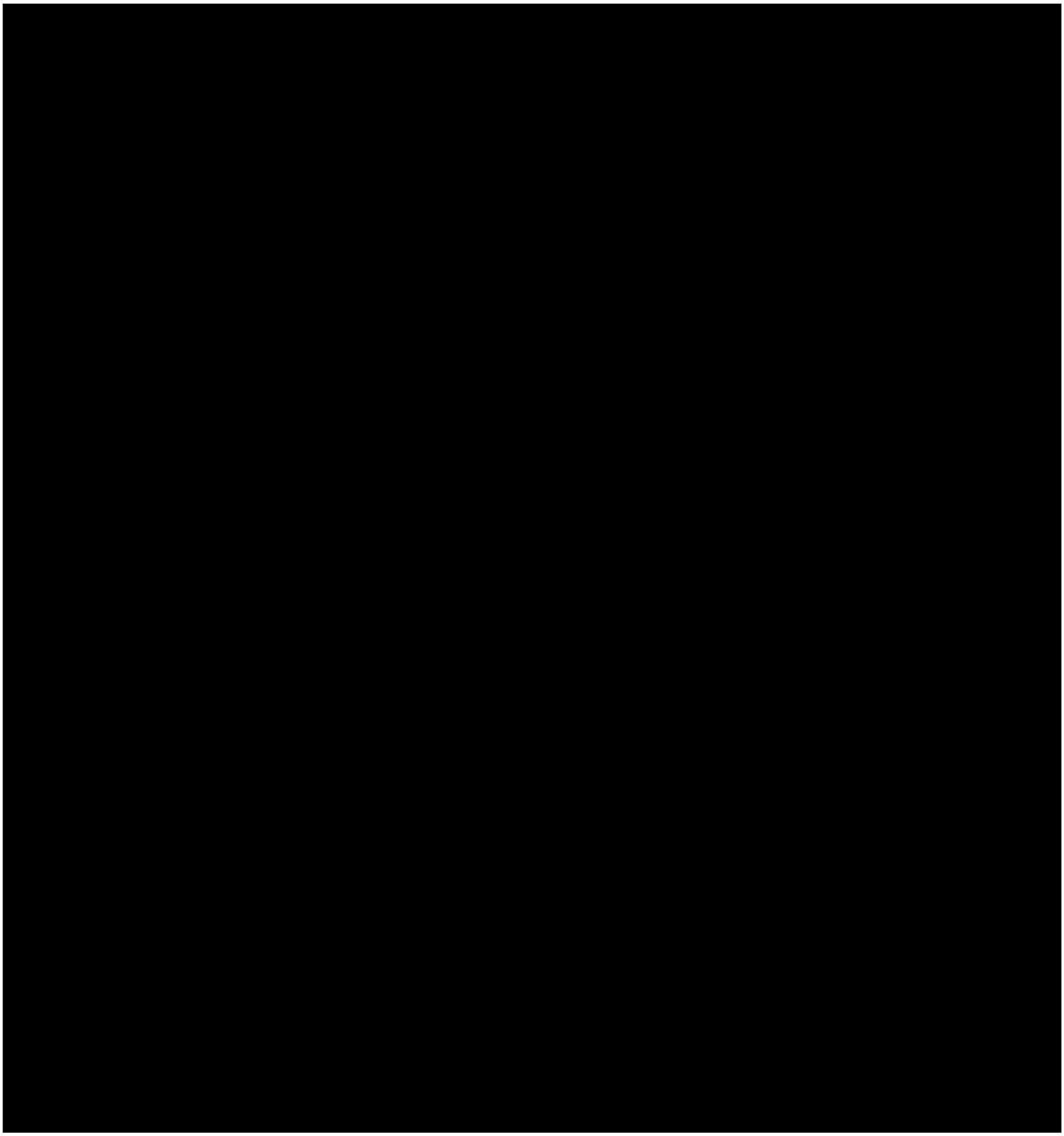
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Minimally Invasive Fetoscopic Repair

The MOMS trial data[1] suggested that approximately 80% of pregnancies were delivered preterm, 25% had membrane separation, and about 30% had thin or dehisced uterine incisions. As a result, the vast majority of fetal surgeons have championed moving towards and / adopted a fetoscopic approach to MMC repair. Dr. Papanna, together with a team of surgeons and his research team at The Fetal Center at CMHH and the McGovern Medical School at UTHealth, has investigated the optimal approach to fetoscopically repair spina bifida defects whilst simultaneously incorporating the use of the NEOX Cord 1K® patch.

The team has generated an *in-vitro* model system to investigate optimal watertight closure methods of various defect sizes using differing suture materials, techniques, and patch types (unpublished data). Briefly, CSF pressures were measured during *in-utero* spina bifida repair of five 24 week GA cases (Figure 13A), followed by designing an *in-vitro* apparatus to mimic those results (Figure 13B). The model consisted of chicken thighs, simulating fetal tissue, which was attached to the base of a column holding between 6-12 cm of water. Wound widths emulating minimal and moderate edge tractions were generated in order to test various suturing techniques

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for primary closure of the defects. Three patches, including the HUC patch, were tested to repair 15 x 15 mm defects using various suturing materials and techniques. Regardless of suture material or method, we found that minimal wound traction provided better seals than moderate wound edge traction in 66 primary closure experiments (Figure 14A-D). Locking sutures improved upon watertight closures in the patch-based systems when compared to non-locking suturing methods (Figure 15).

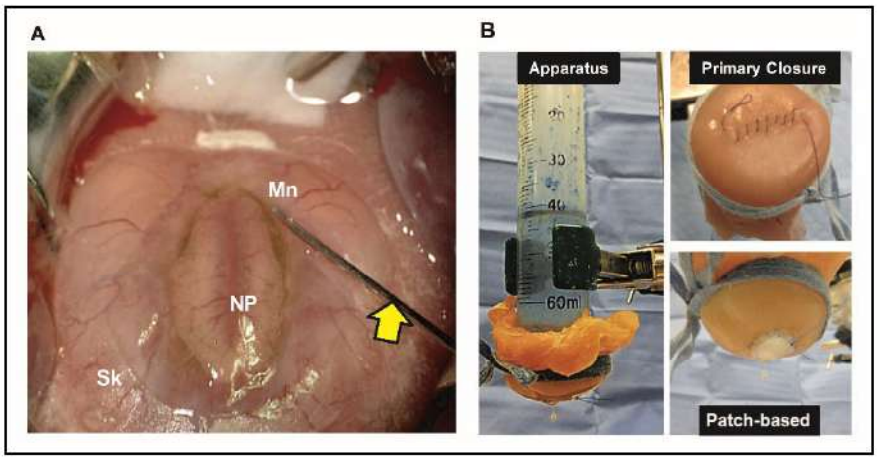
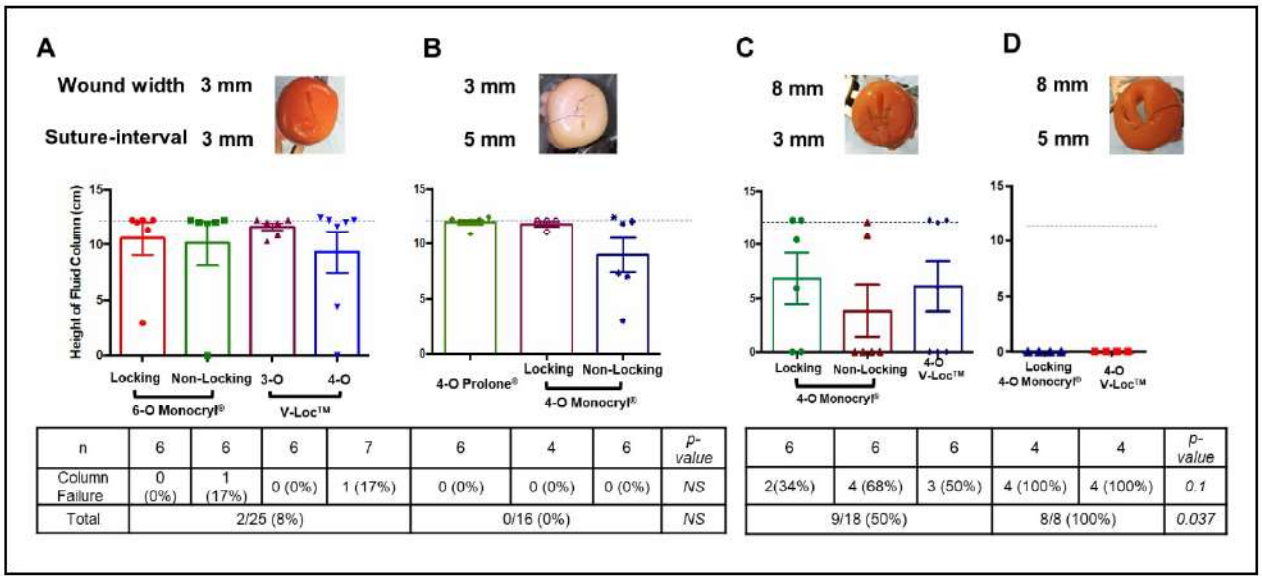


Figure 13. Measurement of CSF pressure and depiction of the *in-vitro* model. (A) Image of needle entry into the myelomeningocele sac immediately after surgical exposure. A 20G needle was inserted into the sac free of the neural placode, followed by connection of the needle to an arterial pressure monitor. The final pressures were read after the measurements were stable for 15 seconds. NP-Neural placode, Mn- Meningeal sac, Sk- skin. **(B)** *In-vitro* model to test for the water tightness of various suturing methods. The apparatus consisted of a 60 cc syringe without a plunger where the chicken thigh could be tied. The defect was created using a scalpel in a standardized manner. For suture-based closures, the defect was closed by approximating the edges with the tension of the suture at different entry points. For the patch-based closure, the patch was cut 0.5 mm larger in length and width than the defect that measured 15 x 15 mm, and was sutured circumferentially to the edges of the defect.

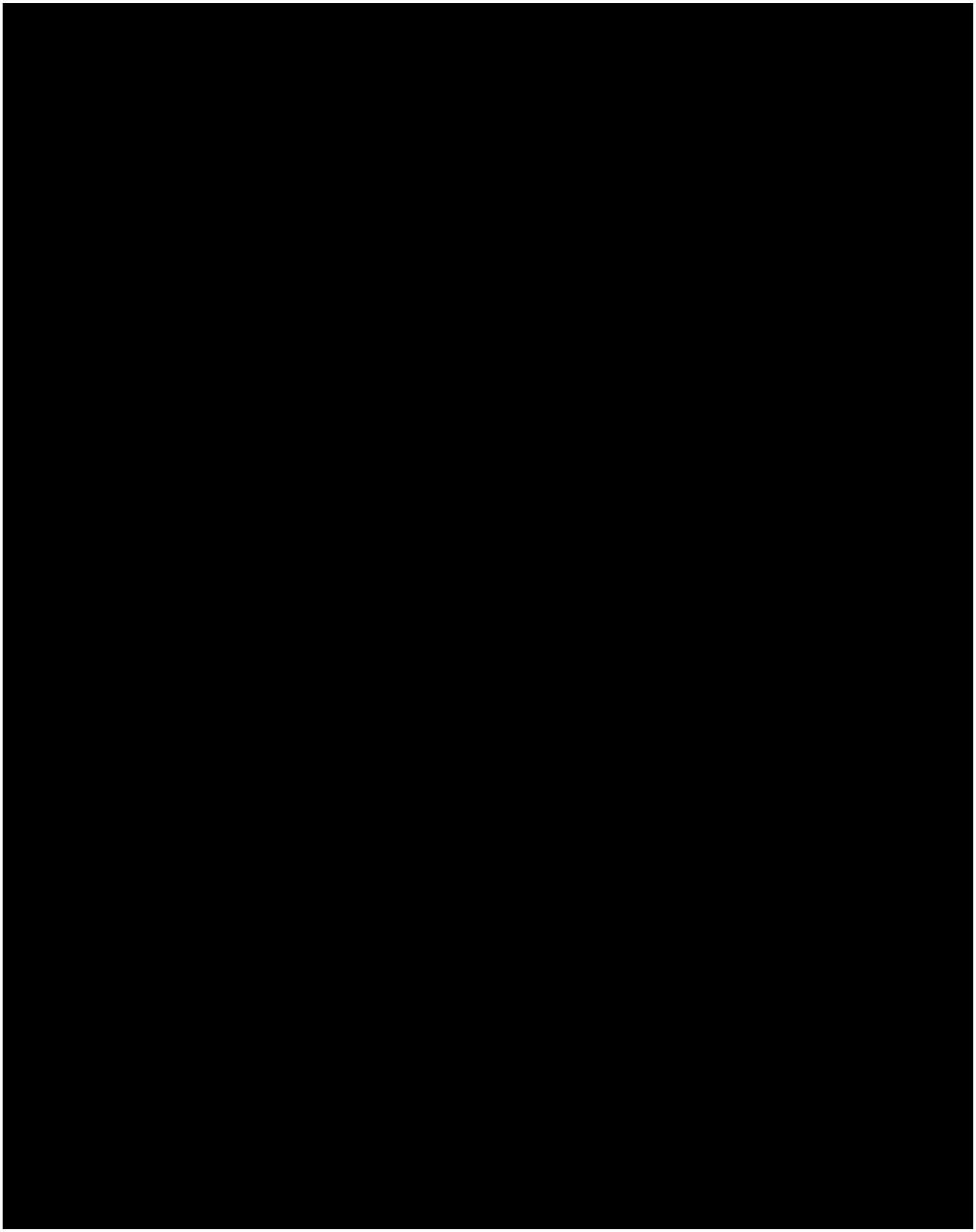


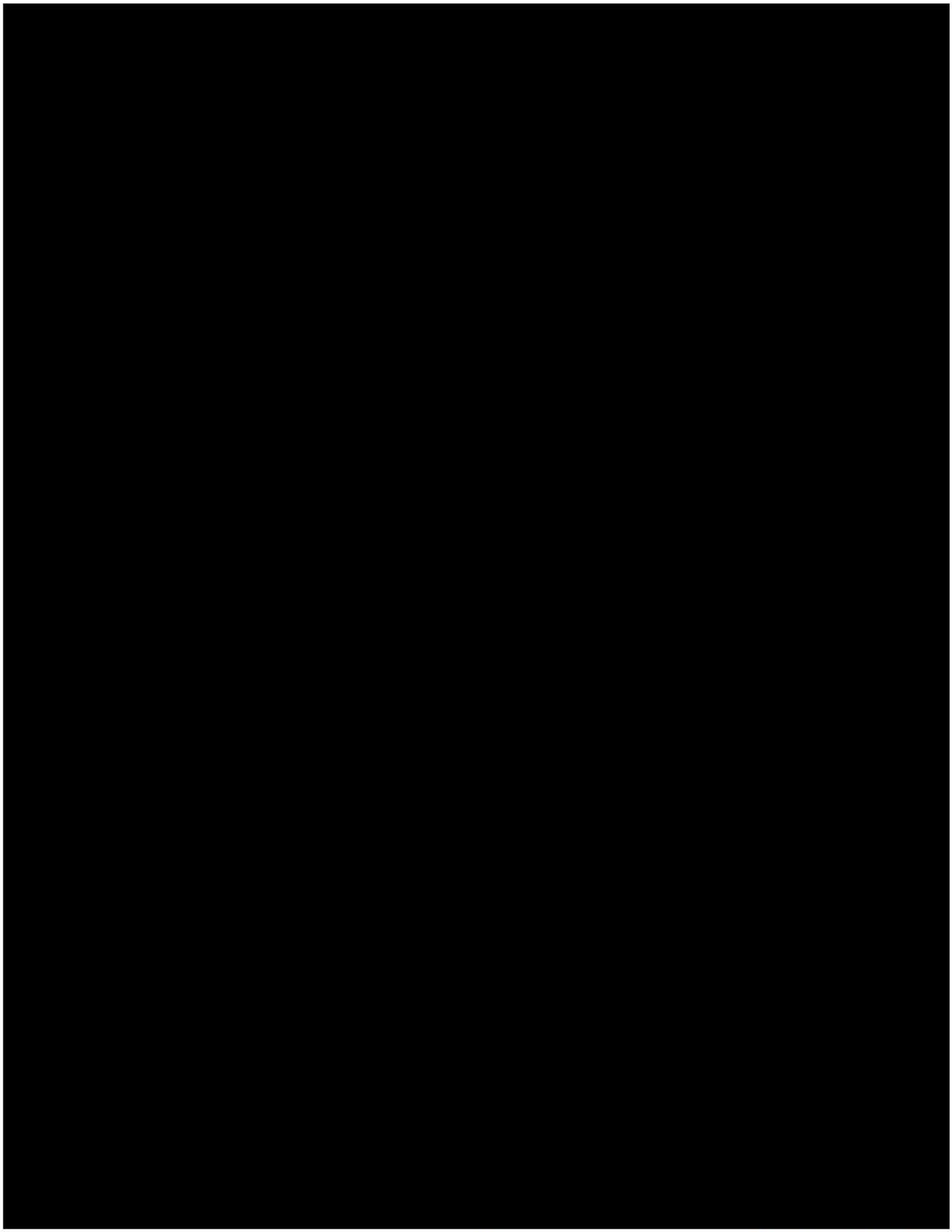
n	6	6	6	7	6	4	6	*p-value*
Column Failure	0 (0%)	1 (17%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	*NS*
Total	2/25 (8%)				0/16 (0%)			*NS*

6	6	6	4	4	*p-value*
2(34%)	4 (68%)	3 (50%)	4 (100%)	4 (100%)	*0.1*
9/18 (50%)			8/8 (100%)		*0.037*

Figure 14. Primary closures of various defect sizes and differing suture intervals. (A) Closures of 3 mm wide defects with a 3 mm suture interval. **(B)** Closures of 3 mm wide defects

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[redacted]

2.3 Risk to Benefit Assessment

2.3.1 Known Potential Risks

There are potential risks associated with *in-utero* surgery to the mother and fetus. The risks associated with a fetoscopic approach are similar to the open approach, which includes preterm premature rupture of membranes, preterm birth, placental abruption, maternal wound infection, chorioamnionitis, fetal membrane separation, amniotic fluid leakage, oligohydramnios, maternal death, and the risk of subsequent infertility. However, recent studies have shown that the preterm premature rupture of membranes and preterm birth rates are lower with the fetoscopic approach compared to the open approach. There is risk of bleeding from the surgery site for both mother and fetus, which may require blood transfusions.

Maternal intraoperative risks include exposure to anesthesia and tocolysis leading to pulmonary edema, and hypovolemia. Other potential risks include preeclampsia, rupturing of the hysterotomy site, thrombosis, hypertension, and abnormal implantation of the placenta in a subsequent pregnancy. Side effects of drugs used for reducing uterine contractions and preterm labor such as magnesium sulfate, Indocin and nifedipine.

Fetal postoperative risks are associated with the potential for preterm birth, including sepsis, respiratory distress, intraventricular hemorrhage, periventricular hemorrhage, periventricular

leukomalacia, necrotizing enterocolitis, CSF leakage, wound dehiscence, and death. These risks are similar to open in-utero spina bifida repair. Other risks include postnatal tethered cord, the possible need for detethering surgery, no biological response after treatment, the failure to reverse hindbrain herniation, graft displacement from the suture site, morbidity after birth associated with spina bifida, and shunt placement.

Fetal intraoperative risks include potential damage to the spinal cord or adjacent structures, intrauterine infection, asphyxia from cord occlusion, oligohydramnios associated with early delivery, and complications associated with anesthesia/medications. Additional risks associated with the fetoscopic approach is the inability to close the defect, or the possibility of wound dehiscence after the repair. If the fetoscopic closure is not feasible, a hysterotomy followed by an open repair will be performed.

In-utero exposure to the CO_2 gas has shown to be safe for short-term outcomes, however, the long-term outcomes including neurodevelopmental effects remains to be seen. The surgical time in the fetoscopic approach is longer than the open approach. Prolonged exposure of general anesthesia to the fetus has had damaging effects in animal studies, however similar effects have not been demonstrated in humans.

[redacted]

[redacted]



The risk to benefit ratio is favorable, supporting the conduct of the study.

3. OBJECTIVES

3.1 Primary and Secondary Objectives

The primary objective is successful surgical closure of the spina bifida defect when repaired fetoscopically with cryopreserved HUCs (NEOX Cord 1K®). The secondary objective is to assess the intact repair of the defect, the prevention of CSF leakage and if wound dehiscence has occurred, at birth and at 12 months of age. These primary and secondary objectives are listed below:-

Primary Outcome Measures:

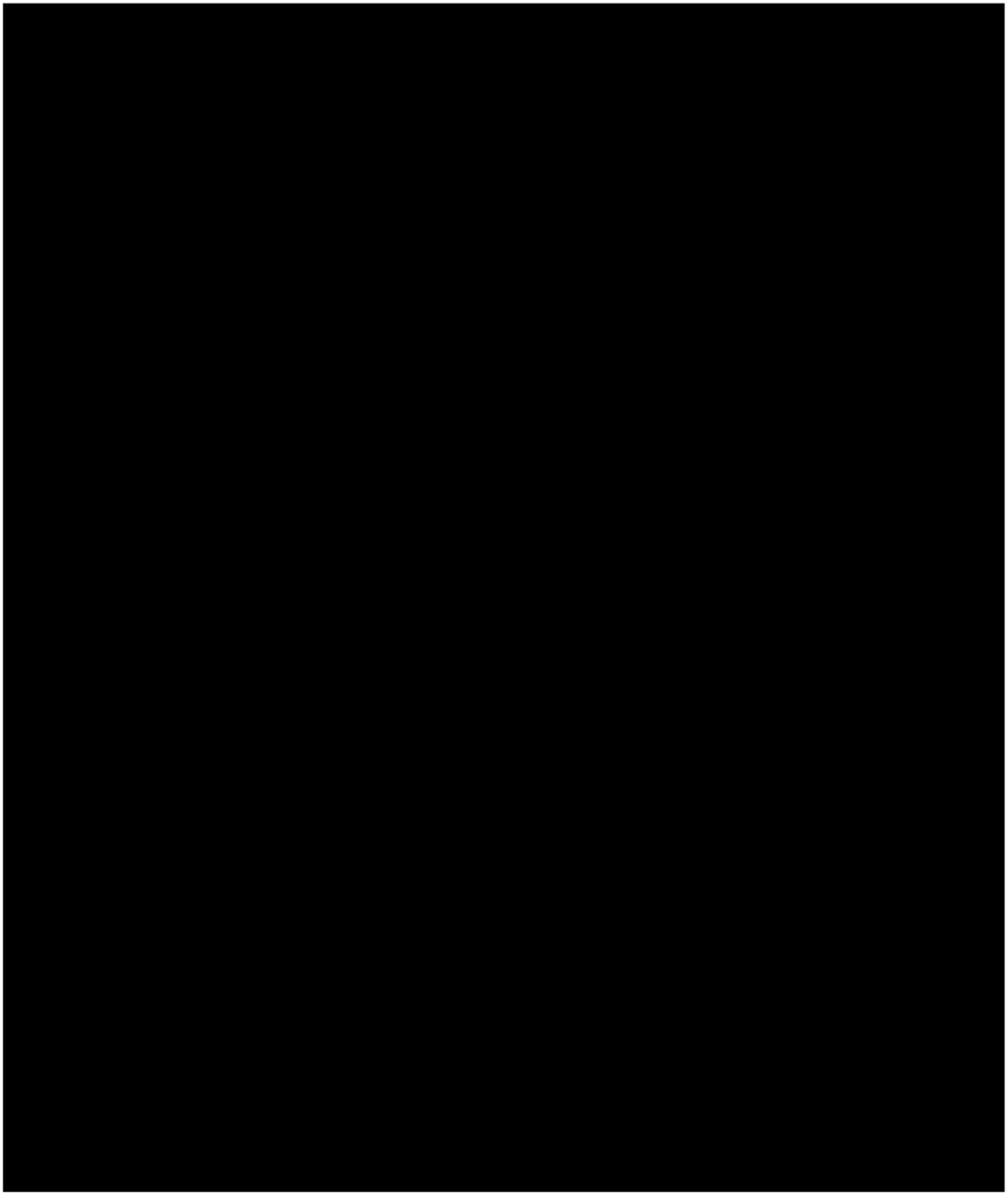
1. Number of patients with successful fetoscopic repair of the defect using NEOX Cord 1K®
   [Time Frame: Immediately after the repair procedure]

Secondary Outcome Measures:

1. Number of patients with intact repair of the defect, defined as no cerebrospinal fluid leakage and no dehiscence at the repair site. [Time Frame: Birth]
2. Number of patients with intact repair of the defect as defined as no cerebrospinal fluid leakage and no dehiscence at the repair site. [Time Frame: 12 ± 2 months]







4. STUDY DESIGN

4.1 Overall Design

This Phase 1 clinical trial will be conducted to test the feasibility of fetoscopically repairing SB defects using cryopreserved NEOX Cord 1K®. The successful fetoscopic repair of the defect using NEOX Cord 1K® is the primary outcome measure. Complete wound closure, no wound dehiscence and no CSF leakage at birth and at 12 ± 2 months of age following fetoscopic *in-utero* SB repair using NEOX Cord 1K® are key secondary objectives.

This is a single site prospective study with a 50 patient core subject population with a spina bifida skin defect. Skin defect sizes will be accurately measured by ultrasound during the gestational age of 19^0 – 25^5 weeks. All eligible subjects meeting all of the inclusion criteria but none of the exclusion criteria will be eligible for study enrollment. Patients will be scheduled for surgery no sooner than gestational week 22^0, and no later than 25^6 weeks gestation.

All eligible pregnant mothers with an eligible fetus will receive NEOX Cord 1K® fetoscopically as a spinal cord cover to repair the defects *in-utero*. *In-utero* repair efficacy has been demonstrated in a randomized, multi-center, controlled trial (MOMS) under support from the NIH, and the benefits of fetoscopic SB repair demonstrated by a number of research teams (Table 5). The outcome of the present study will be compared to the historical controls as detailed in Table 6.

In brief, the surgery will be performed by either Ramesha Papanna, M.D., M.P.H., Anthony Johnson, D.O., or Eric P. Bergh, M.D. in collaboration with a pediatric neurosurgeon Steven A. Fletcher, D.O., and with pediatric surgeons Kuojen Tsao, M.D., and / or Mary Austin, M.D. at UT CMHH.

Under general anesthesia and tocolysis, *in-utero* repair starts with a laparotomy, followed by exteriorization of the uterus and external cephalic version to position the fetus. Uterine entry will be accessed using 3 cannulas, followed by heated-humidified carbon dioxide insufflation for visualization. Fetoscopically, the placode will be dissected and the lesion repaired. NEOX Cord 1K® (HUC) will be used for meningeal closure over the spinal cord, followed by closure of the fetal skin layer. Closure of the fetal skin layer may be achieved primarily or through the use of NEOX Cord 1K® at the discretion of the Pediatric Neurosurgeon. Next, the CO_2 will be removed and replaced with saline or with Lactated Ringers Solution. Finally, the fetoscopic hysterotomy sites will be sutured, and the laparotomy site closed in multiple layers.

Comparisons will be performed to determine if either statistical superiority or non-inferiority exists for an efficacy endpoint between the study patients with prenatal fetoscopic surgery plus NEOX Cord 1K® treatment (i.e., treatment group; and or subgroups) and the historical control patients treated with prenatal surgery (MOMS trial and the University of Texas, Houston, site experience; Table 7). In addition, superiority will be assessed for the overall success of an efficacy parameter if non-inferiority to a historical control has been demonstrated.

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Table 7. Control groups for data analyses.

Prospective Study Arm	Historical Control Arms	
Treatment Group (n=50)	MOMS Prenatal Group (n=78)	UT Houston Historical Group (n=111)
Eligible patients receiving fetoscopic prenatal surgery with NEOX Cord 1K®	All patients in the MOMS trial	All patients that underwent *in-utero* open spina bifida repair

[redacted]

4.3 End of Study Definition

A subject will have completed the study if all phases of the study, including all visits and procedures, are concluded as shown in the Schedule of Activities (Section 1.3).

5. STUDY POPULATION

The target population are fetuses with a myelomeningocele or myeloschisis spina bifida defect as assessed by ultrasound and MRI during the gestational age of 19^0 – 25^5 weeks of gestation that meet all study inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria, Screening

Each eligible subject must meet all the following criteria (modified from the MOMS trial):

Maternal inclusion criteria

1. Singleton pregnancy
2. Gestational age at screening is 19 to 25 5/7 weeks and gestational age at surgery is 22 to 25 6/7 weeks. If the patient's last menstrual period (LMP) is deemed sure and her cycle is 26 to 32 days, and if the biometric measurements from the patient's first ultrasound confirm this LMP within the standardized ranges, the LMP will be used to determine gestational age. In all other cases (i.e. if the LMP is unsure, if she has an irregular cycle or her cycle is outside the standard 26-32 day window or if the measurements from her first ultrasound are discrepant from the ultrasound, the ultrasound determination will be used.
3. Maternal age 18 years and older.

4. Body mass index <40 kg/m^2
5. No risk factors for preterm birth (short cervix, history of previous preterm delivery)
6. No previous uterine incision in the active uterine segment
7. Willing to undergo an open fetal repair if the fetoscopic approach is unsuccessful

Fetal inclusion criteria

1. Spina bifida defect between vertebral levels of T1 to S1 confirmed by ultrasound
2. Chiari II malformation on MRI
3. No evidence of kyphosis (curved spine)
4. No major life-threatening fetal anomaly unrelated to spina bifida. Anomalies such as small ventricular septal defects, polydactyly or cleft lip or palate will be considered for the surgery
5. Normal karyotype or a normal CMA, or a normal CMA with a variant of unknown significance by amniocentesis.
   [Note]: Results by fluorescence in situ hybridization (FISH) will be acceptable instead if the patient is 24 weeks or more.

5.2 Exclusion Criteria, Screening

Subjects who meet any of the following exclusion criteria will not be enrolled in the trial:

Maternal exclusion criteria

1. Non-resident of the United States
2. Multifetal pregnancy
3. Poorly controlled insulin dependent pregestational diabetes
4. Poorly controlled A2DM insulin-dependent diabetes
5. Current or planned cerclage or documented history of incompetent cervix
6. Placenta previa or placental abruption
7. Short cervix < 20 mm measured by cervical ultrasound. The patient may be excluded based on an ultrasound report during initial screening or based on the cervical length measurement performed at the final evaluation.
8. Obesity as defined by body mass index of 40 or greater
9. Previous spontaneous singleton delivery prior to 37 weeks
10. Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia
11. Maternal HIV or Hepatitis-B status positive because of the increased risk of transmission to the fetus during maternal-fetal surgery.
    [Note]: If the patient's HIV or Hepatitis B status is unknown, the patient must be tested.
12. Known Hepatitis-C positivity.
    [Note]: If the patient's Hepatitis C status is unknown, she does not need to be screened.
13. Uterine anomaly such as large or multiple fibroids or mullerian duct abnormality that is diagnosed via imaging prior to surgery, which cannot be avoided during surgery.
14. Other maternal medical condition which is a contraindication to surgery or general anesthesia.

[Note]: This includes any patient with a previous hysterotomy in the active segment of the uterus (whether from a previous classical cesarean, uterine anomaly such as an arcuate or bicornuate uterus, major myomectomy resection, or previous fetal surgery).

15. Patient does not have a support person (e.g., husband, partner, mother)
16. Inability to comply with the travel and follow-up requirements of the trial
17. Patient does not meet other psychosocial criteria (as determined by the psychosocial interviewer using a standardized assessment) to handle the implications of the trial
18. Participation in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial in a previous pregnancy
19. Maternal hypertension which would increase the risk of preeclampsia or preterm delivery (including, but not limited to: uncontrolled hypertension, chronic hypertension with end organ damage and new onset hypertension in current pregnancy)
20. Women who test positive for Zika
21. Allergy/history of drug reaction to Amphotericin B

Fetal exclusion criteria

1. Major fetal anomaly not related to a spina bifida defect. A fetal echocardiogram will be conducted before randomization and if the finding is abnormal, the patient will be excluded.
2. Kyphosis in the fetus of 30 degrees or more
3. Ventriculomegaly greater than 15 mm with no movements noted at hip and knee joints.

5.3 Lifestyle Considerations

Patients need to have a mobile phone and be reachable.

5.4 Screening Failures

Screening failures are defined as participants who have consented to participate in the clinical trial but reported false information that would have excluded them from the trial. Screen failure information that is required to ensure transparency and reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities, will be collected. This reported information will include the patient's demography, details of the screen failure, their eligibility criteria, and if any SAEs occurred. Patients that fail their screen will not be screened again.

5.5 Strategies for Recruitment and Retention

Recruitment is limited to the pool of women who are referred to our site, The Fetal Center, whom will be evaluated for spina bifida for potentially undergoing *in-utero* repair. The trial will be posted on ClinicalTrials.Gov. Incentives, other than the lodging incentive detailed below, will not be offered, and no advertising is planned.

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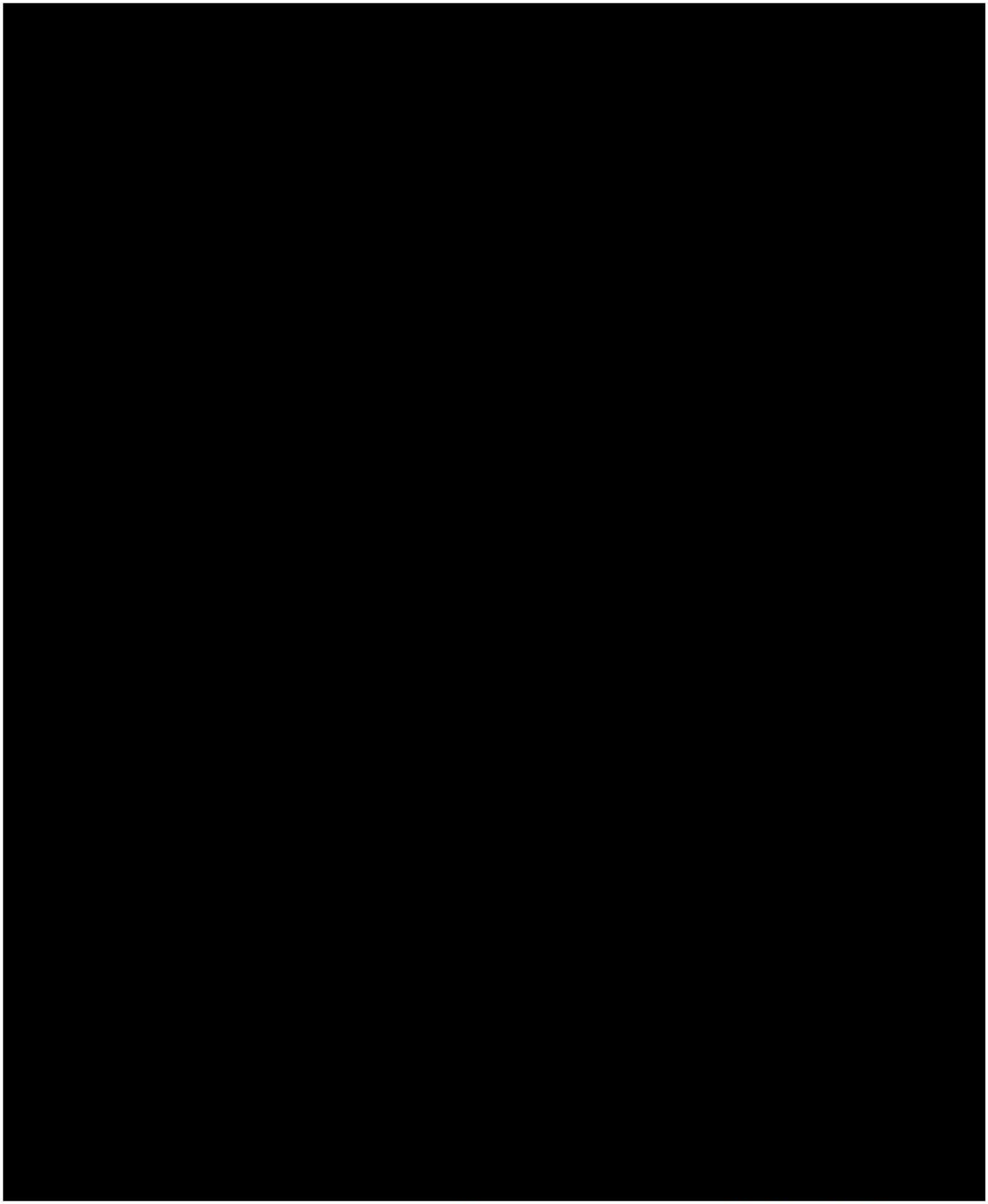
We anticipate that at least 15 eligible patients will be referred to our center per year for spina bifida defects, and that 12 eligible participants will be enrolled per year. Participants will receive timely telephone calls and email reminders of upcoming appointments. If assurances are not received by the patient's local Ob/Gyn physician and the Pediatric Neurosurgeon at the local hospital that they are willing and able to attain the study's required data, in addition to being able to provide the neonate with equivalent NICU care to CMHH, prior to leaving Houston following surgery, the participant will be required to return to Houston at 34 weeks of gestation to facilitate ongoing care through NICU discharge at CMHH. In that case, if the subject is not a resident of Houston proper, accommodation at a Fetal Center contracted corporate hotel will be provided. Accommodation coverage will be from the time relocation is necessary at 34 weeks gestation until the participant delivers, from the time the participant is discharged after giving birth, and up to 2 weeks from delivery.

Additionally, accommodation will be covered during any follow-up visits that span more than a day. If a follow-up appointment is not scheduled at 12, 30, or 60 months of age for the child as part of clinical care covered by their insurance, a research appointment may be scheduled, and the visit will be covered by the research study.



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IRB APPROVAL DATE: 09/26/2024



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6.3 Measures to Minimize Bias: Randomization and Blinding

Since the study is an open-label clinical trial, neither the site's staff or eligible subjects will be blinded. Eligible subjects will be invited to participate by enrolling in the clinical trial. The primary endpoint will be assessed by three independent neurosurgeons for independent verification of myeloschisis cases, and for myelomeningocele cases where the defect is larger than 4 cm.

6.4 Study Intervention Compliance

The study's intervention is the use of NEOX Cord 1K® during the fetoscopic *in-utero* repair of fetal spina bifida defects. Subject compliance is therefore assured, the neurosurgeon and maternal-fetal medicine surgeon's compliance is assured given the assumption that NEOX Cord 1K® is available at the time of the surgery.

6.5 Concomitant Therapy

Appropriate concomitant therapies are allowed for mothers and children that have been prescribed medications for medical problems not related to / or intended to treat the spinal defect other than NEOX Cord 1K® and SOC therapies.

Prohibited medications include the use of other grafts, such as skin grafts and dura patches. If it is determined that the enrolled patient will require another patch material, he/she would discontinue study enrollment but would nevertheless still be followed for safety reasons. Concomitant therapies will be recorded at each study visit from the time of screening until the subject completes the study. This information will be documented in source documents and in the electronic case report forms (eCRFs). Medication given intraoperatively will not need to be recorded in eCRFs as they are a part of SOC procedures.

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6.5.1 Rescue Medicine

Not applicable.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of the study's intervention is not applicable since the use of NEOX Cord 1K® is a one-time application.

7.2 Participant Discontinuation/Withdrawal from the Study/Lost to Follow-up

Study participants have the right to discontinue their enrollment in the clinical trial at any time. All reasons for study withdrawal will be documented in the source documents as well as in the eCRFs. Every effort will be made to ensure that subjects that have elected to discontinue study treatment will be seen at an Early Termination visit. As per the study's protocol, all subjects that withdraw from the study will be followed for the remainder of the study's protocol for safety purposes. Reasons for subject discontinuation from the study's treatment may include a SAE, protocol violation, or the use of a prohibited concomitant therapy. All withdrawn patients that have experienced an AE or SAE will be followed until resolution of the problem or until the unresolved AEs or SAEs are determined by the Investigator to have stabilized. All subjects with unresolved AEs will be contacted one month after their final visit to determine if more information on the event is available.

The Investigator may withdraw a subject from the trial at any time if they deem it medically necessary. Reasons that the Investigator may withdraw a subject withdrawal from the study includes if the subject withdraws from consent, the Investigator terminates the trial, and if the subject is lost to follow-up. If a subject has been removed from the trial or if an AE remains ongoing, the Investigators will follow up with subjects as per their standard medical practice. If a subject is lost to follow-up, a minimum of four contact attempts including three telephone calls and a certified letter will be maintained in the patient's medical records or study file. These contact attempts will be performed in order to reschedule a missed visit and for general counseling on the importance of maintaining assigned visit schedules. If the mother is unreachable, the primary reason for withdrawl from the study will be documented as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Activities by Phases and Visits

8.1.1 Study Screening Phase

[Purpose]: To determine the trial eligibility of the patient by assessing all inclusion/exclusion criteria based on available medical information, clinical assessment, and during the interview of the subject.

Every subject who enters study screening after signing the consent will be assigned a subject ID number for traceability. The subject ID will consist of a 3-digit subject number (i.e. 001, etc.). Any subject who signs an informed consent, but fails to meet the required eligibility criteria is considered to be a screen failure. Screen failure subjects should have their demographic information captured with the reason for failing the screen specified. Patients will not be rescreened.

Potential subjects (pregnant women that are over the age of 18 years) will undergo a comprehensive fetal evaluation at the Fetal Center to confirm the diagnosis of spina bifida defect of ≤4 cm. Study eligibility will be based on the results of the clinical assessments (Table 1). All patients will be screened for trial eligibility by having completed the following procedures at the screening visit (An amniocentesis for genetic results may have been performed prior to the initial screening visit at the Fetal Center, in addition to the Fetal MRI. However, the procedure needs to be performed between 19 to 25 5/7 weeks gestation):

- Obtain informed consent and HIPAA authorization documenting the consenting process
- Obtain the patients' demographics
- Review of medical history
- Documentation of medications that are currently being taken by the subject
- Assessment of all inclusion/exclusion criteria based on the medical information available, clinical assessment, and on the interview with the subject (assessment must be completed by a trained and qualified Investigator)
    - BMI assessment
    - Comprehensive obstetrical ultrasound examination, including documentation of cervical length, gestational age biometry, lesion level, lesion size, lesion type, ventricular size, foot positioning, and lower extremity movement
    - Fetal echocardiogram
    - Fetal MRI to document Chiari II malformation
    - Amniocentesis, or FISH if the patient is at a GA of 24 weeks or more
    - Maternal physical examination and clearance for surgery by anesthesia and by the OB/GYN staff
    - Psychosocial evaluation
- Provide instructions for use of SOC medications

- Schedule the study's intervention procedure visit (must be no sooner than 22^0 weeks and no later than 25^6 weeks gestation)

Patients will undergo detailed counseling for open in-utero spina bifida repair as part of the standard of care. Once they have consented to the procedure, they will be approached to participate in the fetoscopic spina bifida repair and will be consented for the study after explaining the risks, benefits and alternatives.

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

If both a woman and her fetus meets all of the inclusion criteria and none of the exclusion criteria, enrollment into the study will be performed, and the intervention procedure scheduled between 22^0 and 25^6 weeks gestation.

Comprehensive counseling will occur prior to the patient consenting to the study.

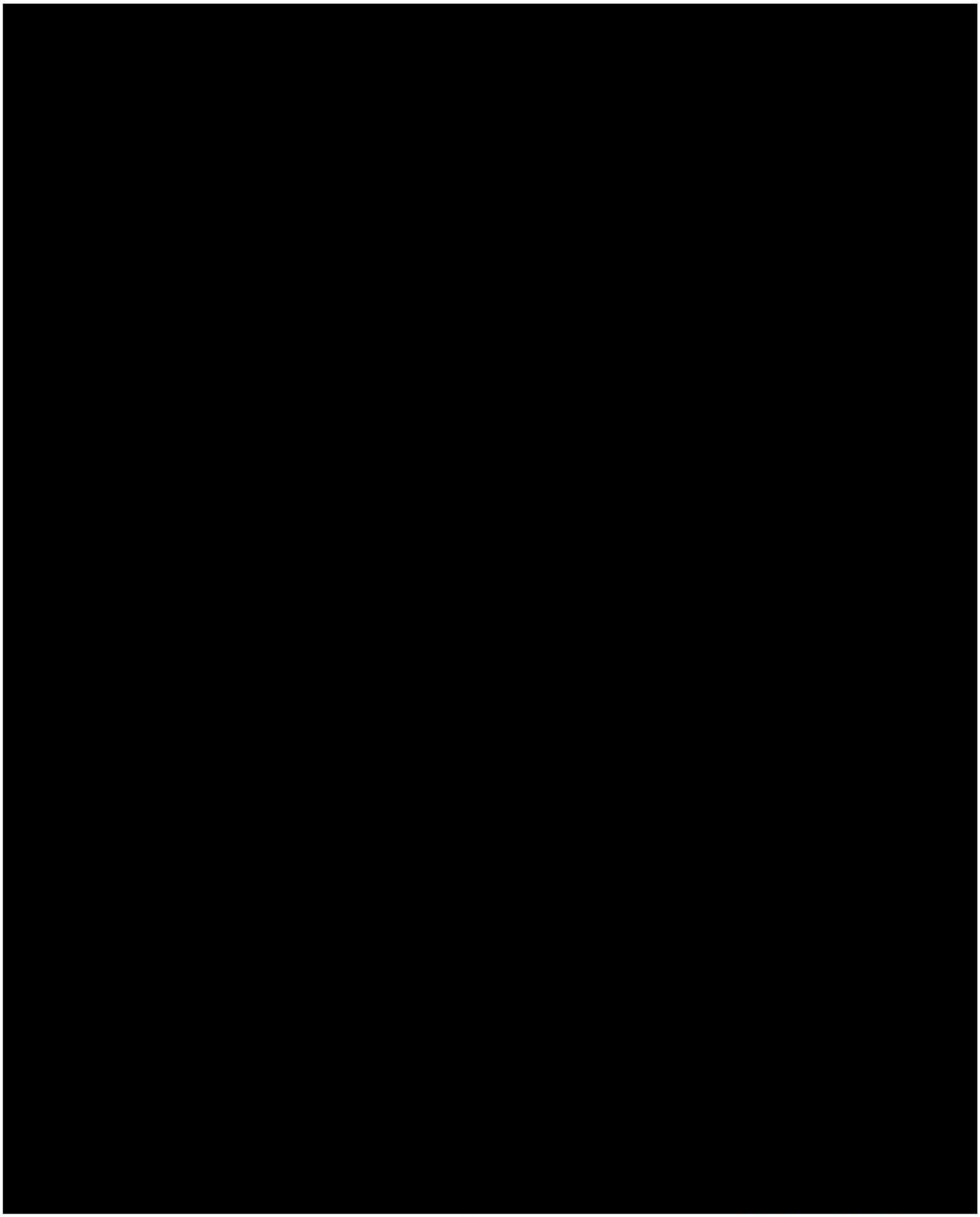
8.1.2 Study Intervention Phase

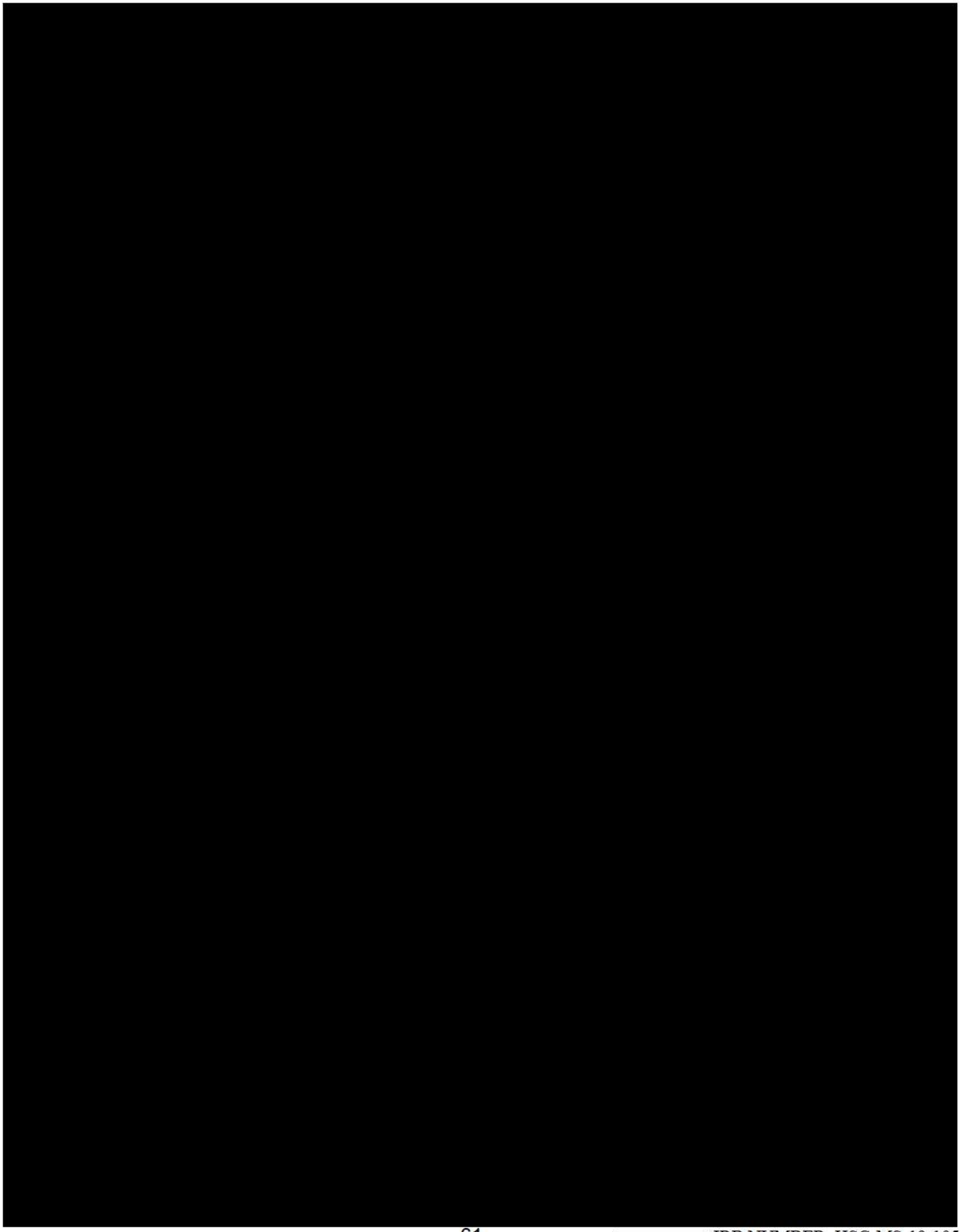
[Purpose]: To perform *in-utero* fetoscopic repair of spina bifida using NEOX Cord 1K® as a meningeal patch to cover the spinal cord with or without the use of NEOX Cord 1K® as a skin patch with standardized Fetal Center preoperative, intraoperative, post-operative care, and delivery procedures.

<u>The following will occur at the procedure visit:</u>

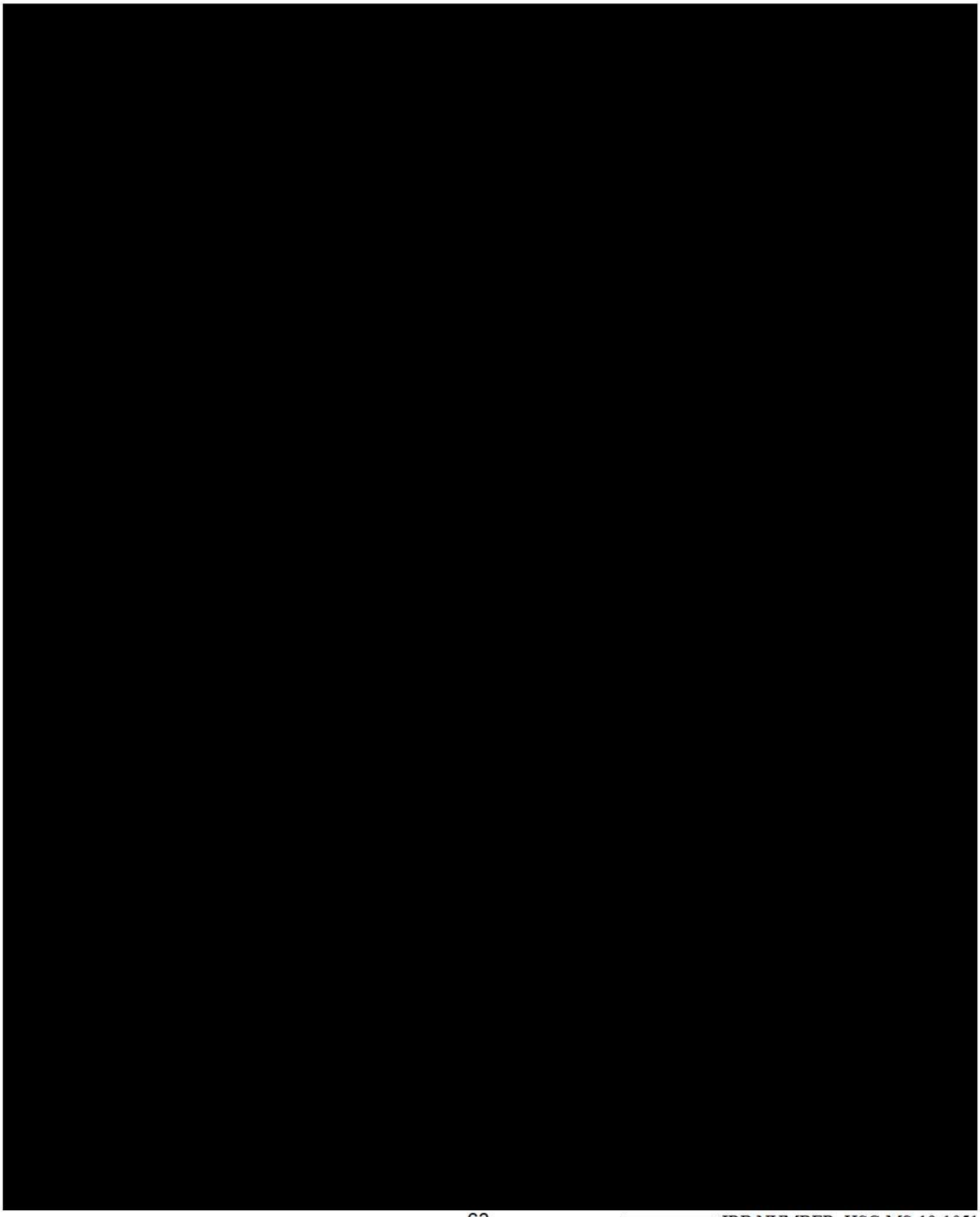
- Collect medication usage including medications given for the procedure
- Query subject to confirm if any AEs have occurred since the screening visit
- Perform fetoscopic *in-utero* repair:
  - Investigators review of all eligibility criteria to confirm the subject still qualifies to participate in the study
  - Application of NEOX Cord 1K® as a meningeal patch
  - Primary skin closure or the application of NEOX Cord 1K® as a skin patch where primary closure of the skin is not possible
- Patient will stay in hospital ~3-5 days or until well enough to leave
  - Daily monitoring for signs of infections, leakage of fluid, PPROM, preterm labor, and pain
  - Daily fetal echocardiograms will be performed while the patient is on indomethacin
- Confirm scheduled appointment for the first post-operative weekly visit

Patient will be placed in supine position under general anesthesia with endotracheal intubation. A midline laparotomy will be performed under sterile conditions. Abdominal wall retractors will be placed and the pregnant uterus exteriorized. Using ultrasound, placental free uterine entry site will be identified. Fetal membranes will be plicated to the uterine wall 1.5 cm apart using delayed absorbable sutures. In between the stiches, an 18G needle will be inserted

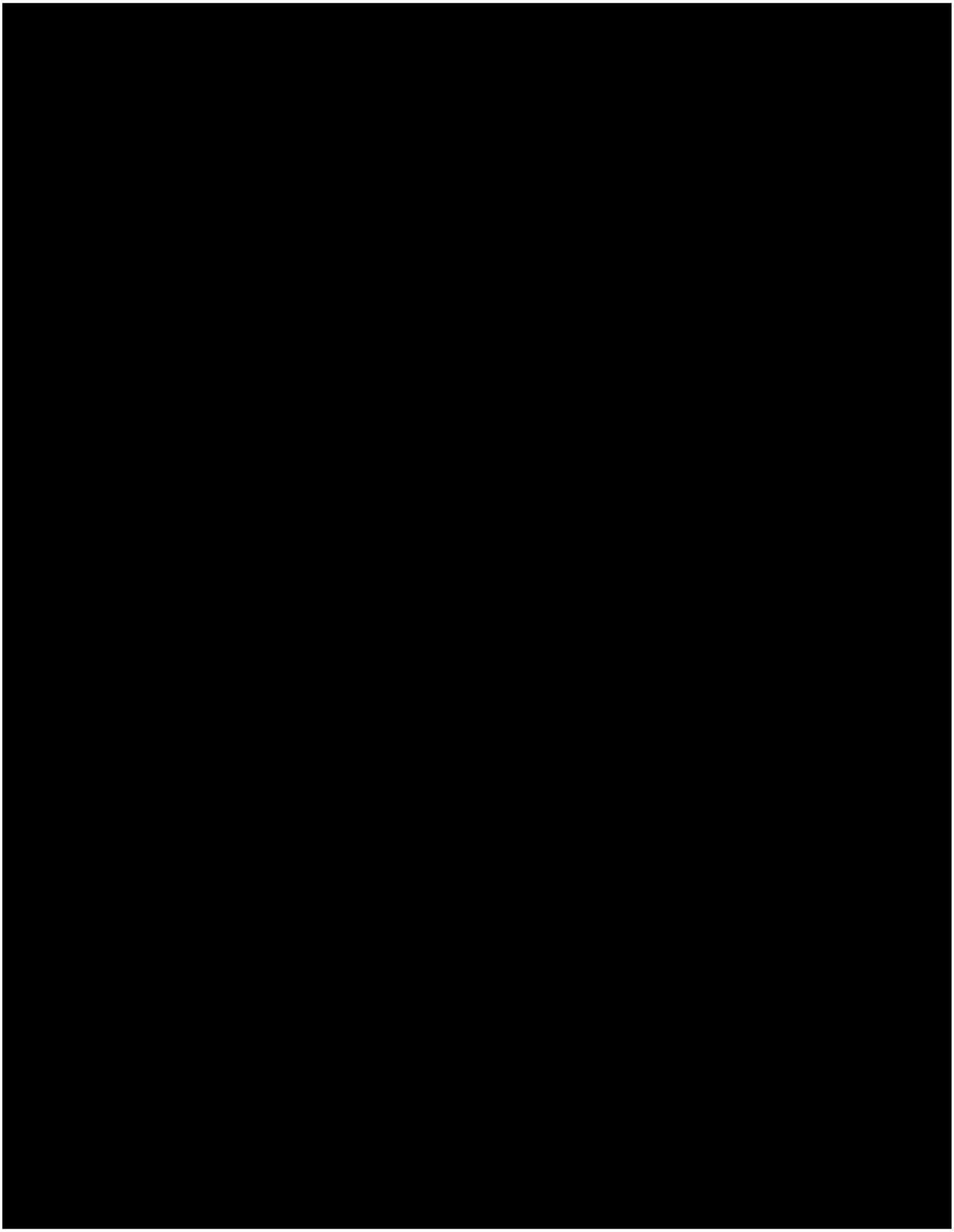


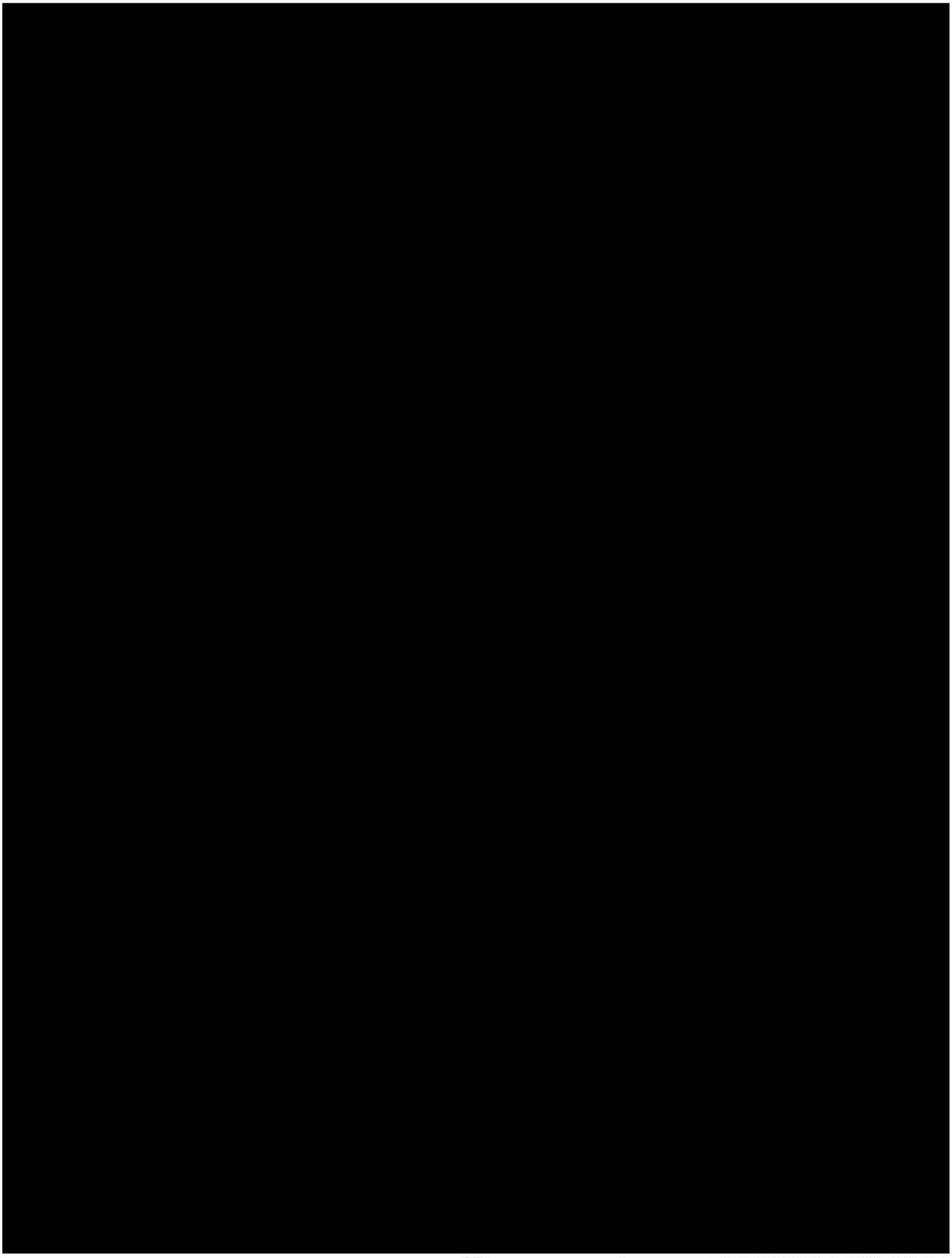


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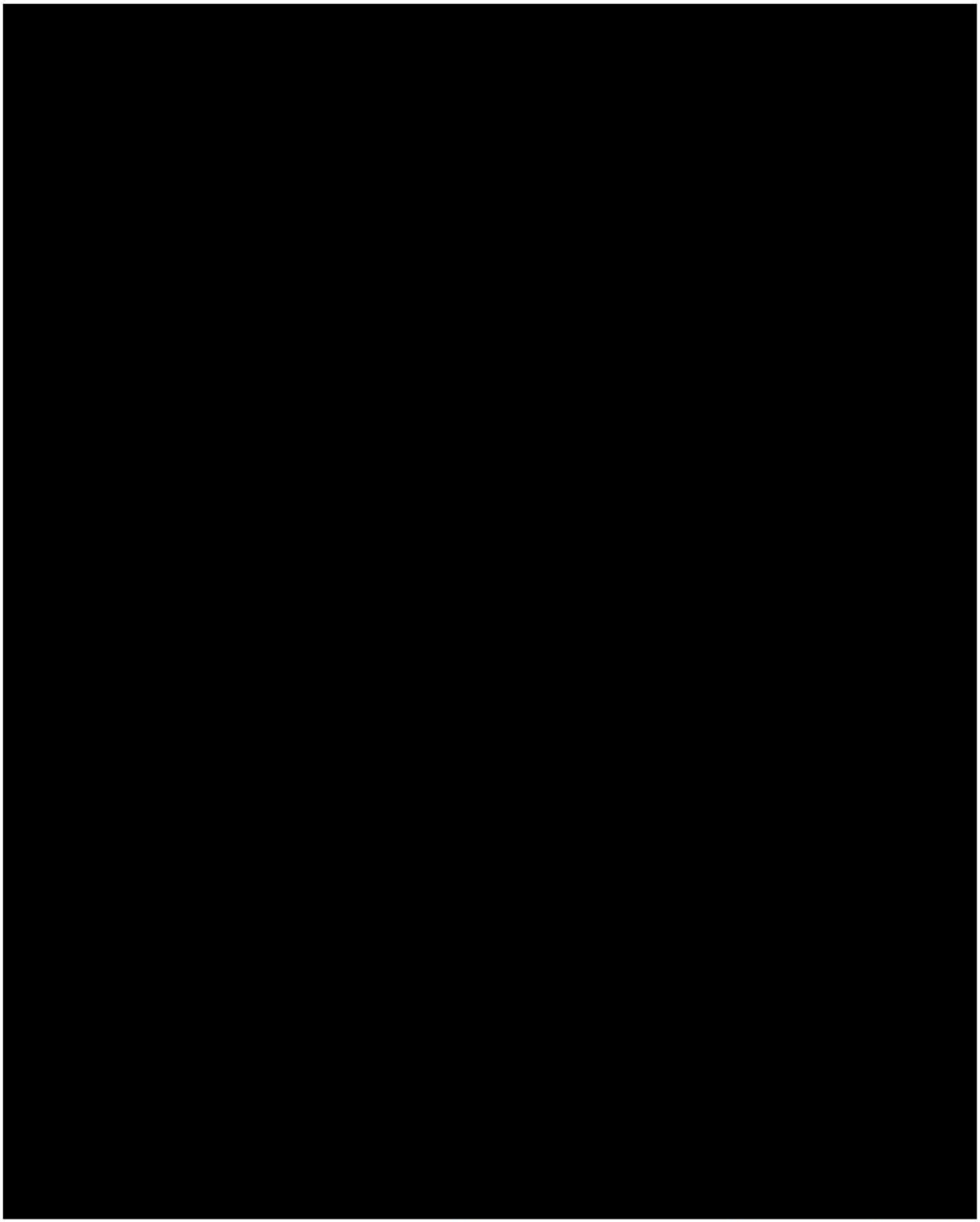


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8.3.1 Definition: Adverse Event (AE)

An adverse event is any undesirable or unintended effect of the research occurring in human subjects as a result of the research or the collection of private health information under the research. 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 SAEs) 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, if the AE is related or unrelated to the surgery, if the AE is expected or unexpected, and whether or not it was an unanticipated problem (UP).

8.3.2 Definition: Serious Adverse Event (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Reporting of SAEs will be based on the FDA's regulatory definitions for studies performed under an IDE, including 21 CFR 812.

8.3.3 Relationship of SAE to Study Intervention

The principle investigator will assess the relationship of an adverse event to NEOX Cord 1K® and/or fetoscopic procedure according to the following definitions:

- **Unrelated:** There is no evidence of any causal relationship.
- **Possibly related:** There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event.

  Probably related: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Definitely related**: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

8.3.4 Expectedness

The principle investigator is responsible for assessing the expectedness of an event. Expected safety events of interest for this study are post-surgical conditions consistent with any *in-utero* SB repair. Below is a list of those events, which include but are not limited to:

Maternal events:

- Chorioamnion separation
- Oligohydramnios
- Placental abruption
- Preterm birth
- PPROM

Fetal and neonatal events:

- Abnormal fetal biophysical profile (<8/10)
- Bradycardia during fetal repair
- Incomplete healing at surgical site
- Necrotizing enterocolitis
- Respiratory distress syndrome
- Retinopathy of prematurity
- Sepsis

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

All unanticipated adverse device effects related or to the study device (NEOX Cord 1K) and/or fetoscopic procedure that meet study definition will be reported to the FDA in accordance with 21 CFR 812.150(a)(1). One such unanticipated problem includes the possibility of infectious agent transmission through the use of NEOX Cord 1K®, or being rejected as an allograft. However, we don't foresee this occurring due to the excellent safety profile of NEOX Cord 1K®.

8.3.5 IRB Notification of SAEs and Other Unanticipated Problems

Serious adverse events that are unexpected, related to the study device or fetoscopic procedure, and put the subjects or others at harm are Unanticipated Problems and need to be reported to IRB within 24 hours of being made aware of the event. Unanticipated problems must be reported via telephone or email to the following representative:

Ramesha Papanna, M.D.,M.P.H.

[redacted]

The event, or outcome of an event, will be reported by the Investigator as soon as the information becomes available. All related documentation will be submitted to the medical monitor for evaluation as soon as it becomes available.

8.3.6 SAE Follow-up Report

If a SAE has not resolved at the time of the initial report, and if 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 and FDA. The Investigator will be responsible for ensuring that all SAEs are followed until they're either resolved or are stable.

8.3.7 Reporting Events to Participants

Not applicable, unless there's a significant health risk.

8.3.8 Reporting of Pregnancy

All pregnancies prior to the 60 month (+ 6 month) visit will be recorded, including outcomes and any complications.

8.3.9 Sponsor-Investigator Reporting to the FDA

The Sponsor-Investigator will report subject outcomes one by one at the time of delivery or if a pregnancy loss occurs.

The Sponsor-Investigator will adhere to all FDA Reporting Requirements under Title 21 CFR 812.150.

Title 21 CFR 812.150 states the following:

"(a) Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor,

the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see 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 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 in accordance with 812.35(a) also is required.

(5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

(b) Sponsor reports. A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) Withdrawal of IRB approval. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) Withdrawal of FDA approval. A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) Current investigator list. A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval

(5) Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress report to all reviewing IRB's and FDA in accordance with 812.36(f) and annual reports in accordance with this

section.

(6) Recall and device disposition. A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator returns, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

(7) Final report. In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) Informed consent. A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) Significant risk device determinations. If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) Other. A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

[45 FR 3751, Jan. 18, 1980, as amended at 45 FR 58843, Sept. 5, 1980; 48 FR 15622, Apr. 12, 1983; 62 FR 48948, Sept. 18, 1997]"

8.3.10 Medical Emergencies

If labor ensues prior to the anticipated delivery date, vaginal delivery may be possible. In the event that delivery occurs at less than 34 weeks, maternal corticosteroids (betamethasone 12 mg intramuscularly and repeated once after 24 hours) will be administered for an impending preterm delivery.

8.3.11 Reporting to the Data Safety Monitoring Committee

The DSMC will be composed of members who are not affiliated with the study's investigation in any manner. The DSMC will not have any formal involvement with study participants or the investigation and will function independently of the sponsor-investigator.

The DSMC will be consulted at any time safety concerns arise during the conduct of the research study. The PI will report the outcome of each case following delivery up to the completed follow-up phase to the DSMC at scheduled semi-annual meetings, or at the discretion of the DSMC. The DSMC will convene semi-annually, in addition to after the first 3 enrolled patients

have delivered and completed the second follow-up phase or one year, whichever is sooner, to review study results.

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

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

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

- Summary of all AEs and SAEs by subject
- Protocol deviations
- New information about the safety of the investigational biological material and / fetoscopic procedure
- Updates to the safety profile of the investigational biological material and / fetoscopic procedure
- External SAEs that are both unexpected and related to the study device (NEOX Cord 1K) and/or fetoscopic procedure (if applicable)
- Protocol amendments

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

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

8.3.12 Recording of Developmental Milestones

One objective of this study is ambulation at 30 months. To properly assess ambulation, the study team will ask parents/guardians to send video recordings of changes to their child's mobility. Communication sent to the research team with images and videos of ambulation and different milestones will be used for future research exploratory analysis. Additionally, research staff will take a video recording of the child walking or mobilizing at the 12 month, 30 month, and 60 month visit time points.

9. STATISTICAL CONSIDERATIONS

9.1 Sample size

This is an early feasibility study to establish feasibility when compared to historical controls or via subgroup analyses. There are no prior studies to calculate a sample size.

9.2 Populations for Analysis

Data from all treated patients will be included in the analysis. Sub-group analyses will be performed as appropriate.

9.2.1 Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will consist of all subjects that received NEOX Cord 1K® as a spinal cord cover, with or without use of NEOX Cord 1K® as a skin cover, for spina bifida during the fetoscopic procedure. The ITT population will be evaluated for all primary and secondary endpoint analyses.

Subjects who received fetoscopic NEOX Cord 1K® repair of their spina bifida defects will be defined as the primary feasibility population. This population will be compared with MOMS and UTHealth's historical control patients, as detailed in Table 6. For smaller patient population subsets, such as myelomeningoceles that have sac diameters greater than 4 cm and myeloschisis cases, subgroup analyses will be performed.

9.2.2 Per Protocol (PP) Population

The per protocol (PP) population are the subset of subjects in the ITT population with no major protocol deviations from the assessments that are detailed in this protocol. Therefore, all ITT subjects found to have major protocol deviations will be excluded from the PP population. All major protocol deviations will be determined by the Principal Investigator prior to locking of the secure REDCap database. PP analyses of primary and secondary efficacy endpoints will be utilized for supportive analyses.

9.2.3 Safety Population

The safety population includes all subjects that underwent *in-utero* repair of spina bifida defects, with or without NEOX Cord 1K® administration. This population will be used for the analysis of safety endpoints.

9.3 Statistical Analyses

9.3.1 General Approach

Data will be presented using summary statistics and / or frequency tables, as appropriate. Treatment group data will be compared to MOMS historical controls in addition to UTHealth's historical controls. Additionally, exploratory subgroup analyses will be performed for the

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myeloschisis cases, and for the myelomeningocele cases that are greater than 4 cm. When presenting results from these two subgroups following exploratory subgroup analyses, if P values are reported, they will be adjusted for multiplicity to control for familywise type I error rates or false discovery rates.

For continuous data, summary statistics will be reported (n, mean, median, standard deviation, and maximum/minimum). Categorical data will be represented using frequency statistics (counts, percentages, observations, scores, levels, and confidence intervals). Demographic sub-groups, including maternal age, gestational age at fetal intervention and / delivery, fetal sex, ethnicity and race, and spina bifida lesion types, namely lesion level, size, myeloschisis, and MMC, will be analyzed. All analyses will be performed at the 95% significance level.

Generalized estimating equations will be used to evaluate longitudinal data, such as for outcomes measured at multiple time points. The proportion of complications for treatment will be reported together with 95% confidence intervals.

Data will be analyzed using SAS Statistical Analysis System Version 9.1.3 or higher, or through the use of other industry accepted statistical analysis software.

Enrollment will include 50 subjects. This is an early feasibility study to determine the feasibility of safely repairing spina bifida defects fetoscopically with NEOX Cord 1K®. Confirmation of feasibility would allow us to proceed with site recruitment for a multi-center study.

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9.3.3 Safety Analyses

The primary safety endpoint is adverse event incidences documented during the study's duration. AEs will be documented during each study visit, or as they occur, and will be descriptively categorized and compared to the MOMS trial.

9.3.4 Baseline Descriptive Statistics

Patients' demographic and baseline data will be collected as follows:

- Maternal age
- Gestational age at delivery of fetus
- Fetal sex
- Maternal ethnicity
- Maternal race
- Fetal ethnicity
- Fetal race

9.3.5 Planned Interim Analyses

Due to the rarity and the severity of this disease, and the open label nature of the study design, along with the limited potential enrollment rate, this will be an adaptive study design that allows for continuous enrollment while the data is analyzed to determine if the study can be terminated early if it achieves statistical significance.

9.3.6 Sub-Group Analyses

Baseline descriptive data will be reported as summary statistics.

9.3.7 Tabulation of Individual Participant Data

Data collected on individual participants during the study's visits will be analyzed as previously detailed.

9.3.8 Additional Endpoints

Additional endpoints of interest are detailed in section 8.2, and are clinically meaningful.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent

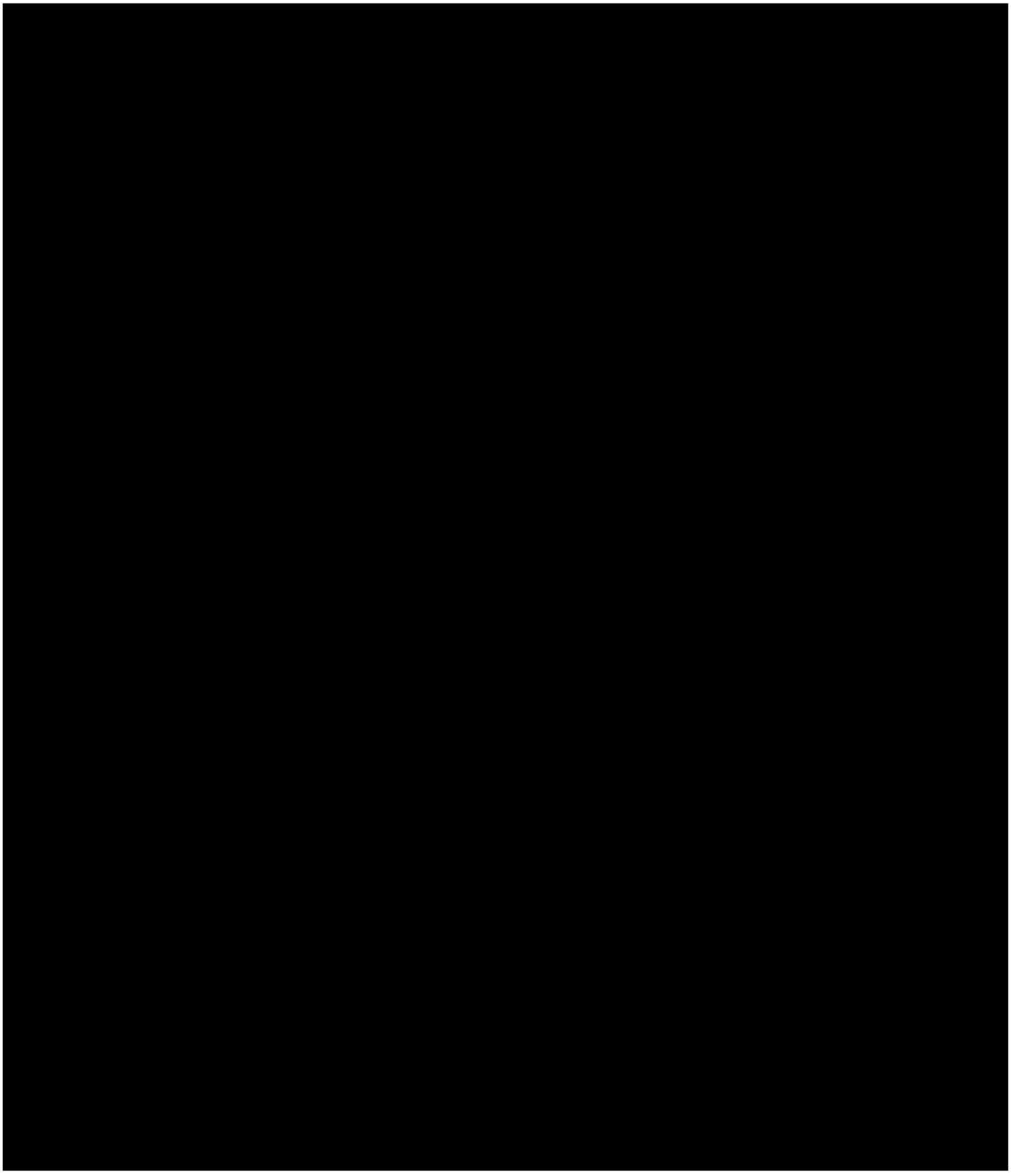
10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

The Memorial Hermann Hospital's informed consent forms are under the authority of the UT IRB (CPHS); therefore we will follow the regulatory mandates set by the UT IRB and their rules for the written informed consent. Any new or amended consent forms will be reviewed and approved by CPHS. Within the consenting process, oral instructions must be given in the patient's native language, and therefore a certified translator will be used during oral discussion.

If eligible, the patient and her family will undergo extensive counseling by Dr. Ramesha Papanna and his team members detailing the study intervention, study procedures, and risks versus SOC procedures will be given to prospective participants prior to the consent process. Consent forms describing the study intervention, study procedures, and risks will be given to prospective participants if they're interested in study participation. It will also be explained to patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The ICF will be in compliance with Code of Federal Regulations (CFR) 21 §50.27 and GCP guidelines. The ICF must be approved by the IRB prior to the start of the study. Each patient's

original signed ICF will be retained in a secure database in the patient's study records, and a copy will be provided to the patient.



[redacted]

10.1.3 Confidentiality and Privacy

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy, and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. In order to protect patient's health information, only study staff, the PI, and co-PIs will have the ability to access any information entered into a REDCap database containing the electronic case report forms (e-CRFs). Each pregnant woman will be coded with a unique study number.

Study consent forms will be stored in the study's regulatory binder and in a UT secure database. The regulatory binder will be stored in a locked cabinet within the research office of TFC. Source documentation for all study data, that is assessments and measurements, will be part of the subjects' medical records (paper and electronic).

Electronic medical records associated with an e-CRF will be stored in REDCap along with the pertinent e-CRF. The PI of the study will apply a digital signature and review date of the medical records within each e-CRF after indicating how many electronic medical records that he has reviewed. Logging within REDCap ensures that any records reviewed cannot be replaced without recording who and when the records were uploaded. If the source document is originally in paper form, a certified copy of the original will be uploaded to the patient's file within REDCap. Information collected for this study includes data abstracted from medical records, procedures, interviews, and tests that are part of this research.

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

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

Scientific publications resulting from this study will not identify any patient by name. Only study staff will have access to the list linking the study code to specific patients taking part in the study. The list will be kept in a double password protected file, located in a research network supported by the Division of General Surgery, separate from clinic charts. All information will be used only for the needs of this study and to evaluate the results.

10.1.4 Future Use of Stored Specimens and Data

This study will not store any specimens.

No identifiable data will be used for future studies without first obtaining IRB approval. The Investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at UT Health Science Center) before sharing a limited dataset,

which may contain dates and zip codes.

Post-hoc analyses may be performed for the purpose of additional reporting of outcomes, or if additional research questions are identified.

10.1.5 Key Roles and Study Governance

Principal Investigator:	Ramesha Papanna, M.D., M.P.H. Associate Professor Program Director, Fetal Intervention Fellowship Research Director, The Fetal Center Maternal-Fetal Medicine Department of OB/GYN UT Health, UT Medical School at Houston [redacted]
Medical Monitor/s:	Susan Wootton, MD

[redacted]

10.1.7 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

A clinical monitor from the Clinical Trials Resource Center will periodically inspect all eCRFs, study documents, and facilities associated with this study independently during and after completion of the study. The monitoring visits will provide the Principal Investigator with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs in REDCap, ensure that all protocol requirements, applicable FDA regulations, and Principal Investigator obligations are being fulfilled, and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Principal Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this trial. The names and identities of all research patients will be kept in strict confidence in REDCap's secure database hosted by UTHealth.

The study's site may also be subject to inspection or audit by the FDA, IRB, or other regulatory agencies.

10.1.8 Clinical Monitoring

The clinical site, namely the Clinical Trials Resource Center (CTRC) will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control procedures will be implemented beginning with the data entry system and data QC checks that will be run on the REDCap database. Any missing data or data anomalies will be communicated to the Principal Investigator.

The monitor from the CTRC will verify that the clinical trial is conducted, and that the data generated and collected, documented (recorded), are reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all regulatory documents, source data/documents, and reports for the purpose of monitoring and auditing of the Principal Investigator for inspection by local and regulatory authorities and the medical monitor. Specifically, this study shall be conducted in accordance with the provisions of the Declaration of Helsinki, FDA regulations 21 CFR 50, 54, 56, and 812, and the ICH guidelines on GCP (ICH E6).

10.1.9 Data Handling and Record Keeping

10.1.9.1 Data Collection and Management Responsibilities

Subject data will be collected and entered by authorized research staff in the Research Electronic Data Capture application (REDCap) system which is compliant with 21 CFR Part 11. This is a secure, web-based system, allowing those with permission to access data from any location at any time. The electronic case report forms generated will create a secure, computer-generated, time stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

10.1.9.2 Study Records Retention

The investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10.1.10 Protocol Deviations

This study will be conducted as described in this protocol except for emergency situations in which the protection, safety and wellbeing of the patient requires immediate intervention based upon the judgement of the investigator. Protocol deviations will be recorded with an explanation as well as actions that were taken to mitigate their effects. Deviations that impact the rights, welfare or safety of patients shall promptly be reported to the IRB as required.

10.1.11 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. 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.

The Fetal Center at UTHealth shall retain ownership of all data, and all proposed publications based on the data of this study is subject to the Principal Investigator's approval and requirements.

10.1.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

The Principal Investigator will disclose any and all financial arrangements to the Institution and will take minimize the potential for bias should that become the case through IRB, the DSMB, and institutional reporting.

10.2 Additional Considerations

An environmental impact assessment or a claim for categorical exclusion is no longer required. [§25.34(g)]. Currently nothing is subject to being sold [812.7(b)].

10.3 Abbreviations

AE	Adverse Event
CA	Chorioamniotic
CFR	Code of Federal Regulations
CIC	Clean Intermittent Catheterization
CM	Chiari Malformation
CPHS	Committee for the Protection of Human Subjects
CSF	Cerebrospinal Fluid
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
ETV	Endoscopic Third Ventriculostomy
FDA	Food and Drug Administration
GA	Gestational Age
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HH	Hindbrain Herniation
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
O/E	Observed/Expected
CTRC	Clinical Trials Resource Center
MMC	Myelomeningocele
N/A	Not Applicable
NEC	Necrotizing Enterocolitis
NICU	Neonatal Intensive Care Unit
NS	Not Specified
ONTD	Open Neural Tube Defect

OR	Operating Room
PDA	Patent Ductus Arteriosus
PPROM	Preterm Premature Rupture of Membranes
PVL	Periventricular Leukomalacia
RDS	Respiratory Distress Syndrome
SAE	Serious Adverse Event
SI	Sponsor-Investigator
SOC	Standard of Care
U/S	Ultrasound
USA	United States of America
VPS	Ventriculoperitoneal Shunt
27^0	27 weeks 0 days gestation – an example of an alternative manner in which to indicate gestational age

10.4 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
1.0	01/31/2020	Original Issue	n/a
2.0	06/28/2021	Increased the enrollment numbers to 25 patients	Feasibility was proven in the first 15 patients.
3.0	04/28/2022	1) Inclusion of myeloschisis and larger myelomeningocele defects in the study. 2) Study expansion from 25 to 50 patients. 3) If assurances are received from the patient's local Pediatric Neurosurgeon and OB/Gyn specialists that the data required at delivery and during the NICU period are captured prior to them leaving Houston following the repair procedure, then the patient may deliver under their care.	1) Feasibility of utilizing two patches during a fetoscopic repair in a practice of medicine case has been established. 2) Feasibility was proven in the first 25 patients. 3) The UT Physicians Maternal Fetal Medicine Team and PI of the study, in conjunction with the study's Pediatric Neurosurgeon has successfully managed the care of patients that delivered locally through efficient and effective communication with the systems in place at other institutions.

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11. APPENDICES

Appendix 1. Right of Reference for NEOX Cord 1K®.

Appendix 2. Right of Reference for Insufflow®.

Appendix 3. Right of Reference for Karl Storz Endoscopy-America scopes.

Appendix 4. IRB Information.

Appendix 5. Informed Consent Form.

Appendix 6. FDA Form 3674.

Appendix 7. Sponsor-Investigator's Agreement.

Appendix 8. Sponsor-Investigator's Biosketch.

Appendix 9. Certification of All Participating Investigators.

Appendix 10. Key References in Full.