CHAPTER 20
SECTION 3
DEPARTMENT OF DEFENSE IN-UTERO FETAL SURGICAL REPAIR OF MYELOMENINGOCELE CLINICAL TRIAL DEMONSTRATION

1.0. *PURPOSE*

This demonstration will improve access to patients with fetuses who have a prenatal diagnosis of myelomeningocele; and to assist in meeting clinical trial goals under the Management of Myelomeningocele Study (MOMS) Protocol, in the formulation of conclusions regarding the safety and efficacy of intrauterine repair of fetal myelomeningocele.

2.0. *BACKGROUND*

2.1. *The current state of the medical literature does not allow for a TRICARE benefit for in-utero surgical intervention for myelomeningocele as it is considered unproven. This determination is based on a Blue Cross Blue Shield technology assessment conducted in February 1999, which examined health outcomes resulting from prenatal correction to fetal malformations known to interfere with organ development (in a potentially fatal manner), and surgical techniques for which prenatal corrections have been developed and applied in humans. Because the evidence for in-utero repair of myelomeningocele was too scant, BCBS did not conduct a detailed analysis. Likewise, TMA's December 1999 and October 2001 medical reviews of literature did not reveal any new evidence to justify TRICARE coverage for in-utero surgical repair of myelomeningocele.*

2.2. *On February 13, 2003 (Vol 68, No 30), the Federal Register announced a demonstration project in which the DoD provide TRICARE reimbursement for active duty members, former members, and their dependents to receive prenatal and postnatal surgical intervention for the repair of myelomeningocele under approved National Institute of Child Health and Human Development (NICHD) clinical trial.*

2.3. *The NICHD agreed to sponsor and actively coordinate an unblinded randomized controlled clinical trial program for the evaluation of the safety and efficacy of intrauterine repair of fetal myelomeningocele. Two hundred eligible patients whose fetuses have been diagnosed with myelomeningocele at 16 to 25 weeks' gestation who are at the age of 18 years or older would be screened for enrollment via telephone by the Biostatistics Center (BCC) at George Washington University in Rockville, Maryland, to undergo an initial evaluation. The NICHD program includes sponsorship in three participating Management of Myelomeningocele Study (MOMS) Centers (Vanderbilt University Medical Center in Nashville, the University of California at San Francisco, and Children's Hospital of Philadelphia) where final evaluation and screening will be performed.*

2.4. *Approximately 60,000 TRICARE births occur at the Military Treatment Facilities (MTF) each year. Approximately 40,000 TRICARE births occur in the civilian hospitals. According the Center of Disease Control, in 2001 there were 20.09 cases of spina bifida per 100,000 births; approximately 19 cases would occur annually in TRICARE. This Demonstration Project is projected to have approximately 6 to 16 TRICARE patients with a fetus with a prenatal diagnosis of spina bifida participating in the protocol each year. DoD financing of this procedure will assist in meeting clinical*

goals and arrival at conclusions regarding the safety and efficacy of intrauterine repair of fetal myelomeningocele.

3.0. *POLICY AND ELIGIBILITY*

3.1. *Effective March 17, 2003, the myelomeningocele demonstration is authorized for all eligible DoD beneficiaries including active duty service members selected to participate in the NICHD-sponsored clinical trial for the treatment of myelomeningocele as outlined in the MCTDP Protocol (Figure 20-3-1).*

3.2. *The DoD will cost-share all medical care and testing required to determine eligibility for the NICHD-sponsored clinical trial, including the evaluation of eligibility at the institution conducting the NICHD-sponsored study, except to the extent that these services are covered by other health insurance of the beneficiary, or through grant support from the NICHD to participating institutions.*

3.3. *DoD will cost-share all medical care required as a result of participation in NICHD sponsored clinical trials. This includes purchasing and administering all approved pharmaceutical agents, perioperative, preoperative and postoperative x-ray or magnetic resonance imaging procedures and ultrasound procedures, physical examination, laboratory investigations, surgical interventions, postoperative management, and peripartum medical or surgical interventions including management of complications not otherwise reimbursed under NICHD grant program or beneficiaries' other health insurance if the following conditions are met:*

3.4. *The providers have obtained preauthorization for the proposed treatment before initial evaluation. If a preauthorization was not obtained before the initial evaluation, preauthorization can take place once the referral sheet from the MOMS Center is received. A preauthorization for enrollment will suffice to cover each incidental expense or claim related to participation in the NICHD sponsored trial extending through the duration of the clinical trial. A preauthorization is required even when the beneficiary has other health insurance and must include verification with the NICHD that the patient has been enrolled in the NICHD-sponsored trial; and such treatments are those indicated in NICHD sponsored protocols; and the patient continues to meet entry criteria for said protocol.*

3.5. *The DoD will not provide reimbursement for costs associated with any non-treatment research activities associated with the clinical trial. This includes, but is not limited to:*

- *Data collection activities;*
- *Management and analysis of the data;*
- *Salaries of the research nurses;*
- *Travel to and from participating fetal surgery centers, per diem and hotel accommodation cost.*

NOTE: *These research costs will not be the responsibility of the patient participating in the trial but will be covered by NICHD grant program or the grantee Institution. If travel costs to and from the participating fetal surgery centers are not covered by NICHD grant program, DoD beneficiaries may receive any travel entitlements they are entitled to under the Joint Travel Regulations, the Joint Federal Travel Regulations, or the TRICARE Prime specialty care travel benefit as the case may be.*

3.6. Cost-shares and deductibles applicable to TRICARE will also apply under this Demonstration. For TRICARE Prime enrollees, including those enrolled in USFHP, applicable co-pays will apply, if any.

3.7. The Assistant Secretary of Defense (Health Affairs) approved this DoD demonstration commencing on the effective date of participation, which is the date 30 days after publication of the Notice in the Federal Register, with those enrolled having periodic examinations during a three-year follow-up period.

4.0. APPLICABILITY

4.1. The provisions of this demonstration are limited to those TRICARE-eligible beneficiaries and active duty service members whose fetuses have been diagnosed with myelomeningocele at 16 to 25 weeks' gestation and who are at the age of 18 years or older (on the date of enrollment). The demonstration does not apply to those TRICARE-eligible beneficiaries enrolled in the Continued Health Care Benefit Program (CHCBP), or the military retirees' Federal Employees Health Benefits Program (FEHBP).

4.2. Inquiries and claims related to the Demonstration*'s prenatal protocol*, *ex*cluding claims for *the post-natal* protocol*,* shall be submitted to the *South Region* referencing the Department of Defense In-Utero Fetal Surgical Repair of Myelomeningocele Clinical Trial Demonstration. *All inquiries and claims related to the Demonstration's post-natal protocol shall be submitted to the appropriate regional MCS contractor, as these services are covered under the Basic Program.* The DoD has no authority regarding the NICHD protocol eligibility for the sponsored study. Therefore, if a patient does not meet the criteria for enrollment, appeal rights do not apply.

5.0. GENERAL DESCRIPTION OF ADMINISTRATIVE PROCESS

The regional MCS contractor shall verify the TRICARE eligibility of the patient on the Defense Enrollment Eligibility System (DEERS). Patient selection will be made by the Biostatistics Center (BCC) at George Washington University in Rockville, Maryland in accordance with the protocol. Those patients remaining eligible and interested will be assigned by the BCC to one of the three participating MOMS centers. The contractor will not be involved in medical necessity or clinical review of the Demonstration claims. Claims for approved care under the Demonstration shall be submitted to the *South Region* for adjudication.

6.0. ASD(HA) RESPONSIBILITIES

ASD(HA) is the designated Executive Agent for the Demonstration project. They shall designate a project officer in the Office of the DASD (Clinical Services) for the Demonstration. The project officer shall provide clinical oversight and resolve any clinical issue among DoD, NICHD and MCTDP.

7.0. THE BIOSTATISTICS CENTER (BCC)

For the myelomeningocele clinical trial, the BCC will serve as a referral center for patients and coordinate the outcome evaluations, including both the review of the MRI, and ultrasounds, as well as the infant follow-up examinations. The BCC may be contacted at:

Dr. Catherine Shaer, Program Manager
Management of Myelomeningocele Study (MOMS)
The Biostatistics Center, The George Washington University
6110 Executive Boulevard, Suite 750
Rockville, MD 20852
Call toll-free: 1-866-ASK-MOMS (1-866-275-6667)
Fax toll-free: 1-866-458-4621
http://www.spinabifidamoms.com

8.0. PARTICIPATING MOMS CENTERS

8.1. Participating MOMS centers will be responsible for obtaining information regarding possible third-party liability and other health insurance (OHI) coverage of the TRICARE beneficiary. The MOMS centers shall collect from third party or the OHI and bill any remaining balance of the total amount to the appropriate regional contractor within 30 days of the receipt of the payment from the OHI. The MOMS centers shall ensure proper entry regarding the OHI on the UB-92 claim form before submitting the claim form to the contractor.

8.2. In the event that the MOMS centers are unable to collect from a third party or the OHI for health care services that would be covered under the third party liability or by the OHI if provided by a private provider, no bill shall be presented by the MOMS centers to the DoD contractor. The MOMS centers shall determine patient acceptance for participation in the Demonstration in accordance with the protocol outlined in Figure 20-3-1.

8.3. Participating MOMS centers shall request reimbursement for inpatient services provided under the Demonstration completing a UB-92 and submitting the form to the appropriate regional contractor. Reimbursement will be based on billed charges, which will cover all professional and institutional services. The MOMS centers shall be responsible for collecting the beneficiary cost-shares from TRICARE patients. The participating MOMS centers shall submit all charges on the basis of fully itemized bills. Each service and supply shall be individually identified and submitted on the appropriate claim forms. In cases where care of a TRICARE-eligible patient is terminated under the clinical trial, the MOMS centers shall submit the claims to the contractor within 30 days of such termination.

8.4. The MOMS centers shall establish a POC to respond to inquires related to participation in the Demonstration and for coordination with the regional contractors. Unless otherwise agreed to between NICHD and DoD/TMA, the coordination support by the MOMS centers shall be provided for up to 12 months after termination of the demonstration.

9.0. TMA AND CONTRACTOR RESPONSIBILITIES

9.1. TMA will provide:

- A special fund for the purpose of the demonstration.
- Periodic review and evaluation of the Demonstration claims adjudication process.
- Communications and Customer Service functions to properly inform and periodically update the patient and provider communities regarding the terms of the Demonstration.

9.2. The contractor shall:

9.2.1. Verify the patient's eligibility on the Defense Enrollment Eligibility Reporting System (DEERS). If the patient is authorized to receive the care under the Demonstration, but DEERS reflects that the patient is not eligible, a statement shall be added to the authorization letter indicating before benefits can be paid, the patient must be listed as eligible on DEERS. The patient shall be referred to the personnel/ID Card section of the military installation nearest to his or her home for an eligibility determination. If a patient is listed on DEERS as being eligible as of the date enrollment begins, all services provided as a result of participation in an NICHD sponsored study shall be covered. This also applies to patients whose treatment is in process when the Demonstration expires.

9.2.2. Issue an authorization to the applicant provider and patient once a determination is made regarding eligibility and/or a particular protocol.

9.2.3. Refer eligible patients to BCC for initial screening and protocol information for participation in the study.

9.2.4. Furnish a list of enrollees in the Demonstration to the contractor's Program Integrity Unit with instructions to run an annual post-payment report to determine if hospitals are receiving additional unlawful payments as a result of also receiving payment under TRICARE. If such payment exists, it shall be the responsibility of the contractor to initiate recoupment action for any Demonstration benefits paid in error. This function will be supervised by the TMA Program Integrity Office.

9.2.5. Establish and maintain a database of patients participating in the Demonstration. The database shall include the patient's name, sponsor's social security number, name and number of protocol, treatment, hospital name and address and total cost. The database shall also include the date the TRICARE beneficiary was either accepted, or denied enrollment into the clinical trial and the patient shall be carried on the report until the Demonstration ends. Provide report to the Office of MB&RS, TRICARE Management Activity on quarterly basis, 30 days from the end of the quarter.

10.0. CLAIMS PROCESSING REQUIREMENTS

10.1. Claims under the NICHD clinical trial demonstration project shall be processed by the South Region. Jurisdiction edits shall not apply thereby ensuring that claims are paid and submitted to the TMA in accordance with current requirements for not at risk funds.

10.2. Verify TRICARE-eligibility on the DEERS prior to payment.

10.3. Both institutional and professional charges shall be reimbursed based on billed charges.

10.3.1. The NICHD participating MOMS centers shall submit all charges on the basis of fully itemized bills. Each service and supply shall be individually identified and submitted on the appropriate claim forms.

10.3.2. Claims for medical care required as a result of participation in an NICHD sponsored study for in-utero fetal repair of myelomeningocele or treatment that is not a TRICARE benefit *(i.e., the Demonstration's pre-natal protocol portion)*, shall be processed and paid under the *South Region*.

10.3.3. Cost-shares and deductibles applicable to TRICARE will also apply under the Demonstration. For TRICARE Prime enrollees, including those enrolled in USFHP, applicable co-pays will apply.

10.3.4. The contractor shall query the DEERS Catastrophic Cap and Deductible Data base (CCDD) to determine the status of deductible and catastrophic cap met amounts for TRICARE-eligible beneficiaries at the time the costs are listed on the voucher for processing and payment. The contractor shall determine what expenses to apply to the deductible and catastrophic cap and report these to the CCDD. These expenses shall be reported at the same time the costs are listed on the voucher for processing, prior to payment of the claim.

10.4. Double coverage provisions apply. Acceptable evidence of processing by the double coverage plan is outlined in the TRICARE Reimbursement Manual, Chapter 4. In double coverage situations, the Demonstration will pay the balance after the other health insurance has paid.

10.5. Claims shall be paid from the applicable non-underwritten bank accounts, see Chapter 3, and submitted through normal TEDS processing as required in the TSM with the applicable coding for clinical trials.

10.6. Once in-utero fetal surgical repair of the myelomeningocele becomes a TRICARE benefit, claims for treatment shall be processed and paid based on the regional contractor's implementation date for the change. If a claim spans the implementation date, the contractor shall process and pay those charges on the claim that are prior to the implementation date and the regional contractor shall process the remaining charges under its at-risk contract. The contractor shall notify the provider the claim has been split for processing of charges as of the date of implementation for the TRICARE benefit. If the patient is an inpatient at the time in-utero fetal surgical repair of the myelomeningocele becomes a TRICARE benefit, and the

claim is subject to the DRG-based payment, then the claim cannot be split. Under these circumstances, the entire claim shall be processed and paid under the Demonstration.

10.7. A Nonavailability Statement (NAS) is not required under the Demonstration.

FIGURE 20-3-1 DEMONSTRATION PROTOCOL

MANAGEMENT OF MYELOMENINGOCELE STUDY (MOMS)
A RANDOMIZED TRIAL OF PRENATAL VERSUS POSTNATAL REPAIR OF MYELOMENINGOCELE

Protocol

The National Institute of Child Health and Human Development
Fetal Surgery Units Group

Prepared by the

Data and Study Coordinating Center for the Fetal Surgery Units Group

The Biostatistics Center
The George Washington University
6110 Executive Boulevard, Suite 750
Rockville, MD 20852
(301) 881-9260

September 1, 2002

1 INTRODUCTION

1.1 STUDY ABSTRACT

In the last five years, repair of myelomeningocele in utero has become an established technique. The rationale is that early prenatal intervention may preserve neurological function that would otherwise be lost during gestation. Indeed, data from the first 180 fetuses undergoing this procedure since its inception in 1997, suggest that the incidence of shunt-dependent hydrocephalus may be reduced and the cerebellum and brainstem may be restored to more normal configuration. However, the evidence is far from convincing in that comparisons were made with historical controls and there is very little follow-up data from the children who received the surgery prenatally. A randomized trial, with follow-up of the infants to determine neurological functioning is described. Two hundred pregnant women in the second trimester with the diagnosis of myelomeningocele will be randomized either to prenatal or postnatal repair at one of three fetal surgery units, with follow-up to be conducted by an independent team of examiners.

1.2 PRIMARY HYPOTHESES

Mid-trimester intrauterine repair of fetal myelomeningocele reduces the risk of death or ventricular decompressive shunting compared with standard postnatal repair.

Mid-trimester intrauterine repair of myelomeningocele results in an improvement in neurologic and neuro-motor function compared with standard postnatal repair.

1.3 PURPOSE OF THE STUDY PROTOCOL

This protocol describes the background, design and organization of the study and may be viewed as a written agreement between the study investigators. It is reviewed by the Advisory Board, and is approved by the Steering Committee, the Data and Safety Monitoring Committee and the Institutional Review Board (IRB) of each clinical center and of the data and study coordinating center (DSCC) before recruitment begins. Any changes to the protocol during the study require the approval of the Steering Committee.

A manual of operations supplements the protocol with detailed specifications of the study procedures.

2 BACKGROUND

2.1 INTRODUCTION

Open neural tube defects are a group of congenital abnormalities that arise by day 28 post-conception when some portion of the neural tube fails to close. These defects are the most common and most severe of the congenital abnormalities affecting the central nervous system. Approximately 2,000 fetuses annually are affected with some sort of open neural tube defect in the United States, about half of which are open spina bifida.[1] Health care costs are estimated by the Centers for Disease Control at $200 million per year. Open spina bifida can occur either with a flat defect without a fluid filled sac covering (myeloschisis), with a membranous covering (meningocele), or membranous covering with extrusion of the cord into the sac (myelomeningocele). In most cases it is also associated with hydrocephalus and the Chiari Type II malformation (hindbrain herniation).

Open spina bifida is frequently diagnosed prenatally through the combined results of second trimester maternal serum alpha-fetoprotein screening and obstetrical ultrasonography. Until recently, the only options available to parents once a diagnosis was made prenatally were expectant management with delivery and postnatal therapy for the child, or pregnancy termination. Current neonatal management consists of prompt closure of the defect in an attempt to prevent infection or further injury to the exposed neural elements.

2.2 SEQUELAE OF SPINA BIFIDA

Infant death related to open spina bifida in the United States is estimated at 10% and remains about 1% per year.[2,3,4] Those who survive are likely to experience significant life-long disabilities. Botto and colleagues note, "Medical problems may result from the neurologic defect or from its repair (e.g., paralysis, hydrocephalus, Arnold-Chiari type II malformation, endocrine abnormalities, tethered cord, syringomelia, and syringobulbia) or may be sequelae of the neurologic deficit (e.g., deformations of the limbs and spine, bladder, bowel, and sexual dysfunction, and learning disabilities)."[5] These deficits and problems are related to the spinal cord level of the lesion and the degree of damage to the cord itself during the pregnancy, delivery, and the neonatal period.

The first year of life in a spina bifida child is dominated by neurosurgical interventions, in particular, ventricular peritoneal shunting to control the effects of hydrocephalus, itself a result of hindbrain herniation. Untreated, severe hydrocephalus can lead to brain damage and death. Complications of shunting include blockage or under-drainage, causing the symptoms of hydrocephalus to return, over-drainage that can lead to hemorrhage, and infection. Complications are relatively common and lead to the necessity for shunt revision surgeries.

Later, orthopedic and urologic considerations tend to preoccupy these patients. Nearly 90% of infants with spina bifida have some type of foot deformity such as clubfoot, vertical talus deformity or calcaneovalgus which requires splinting and/or casting followed by surgical repair once weight bearing activities are achieved.[6] Hip surgery in the form of muscle-tendon releases, open reduction of the hip, and proximal femoral osteotomy with or without acetabuloplasty and muscle balancing, is often necessary if the "verticalization" process of the child is inhibited. In addition, the majority of patients with myelomeningocele are

afflicted with some degree of leg weakness resulting from damage to the spinal cord at lumbar and upper sacral levels. The neurologic deficit is usually at or slightly above the level of the last intact vertebral segment. In a study of 101 spina bifida patients by Cochrane,[7] 90% of patients with a thoracic level lesion used wheelchairs and 45% and 17% of patients with a lumbar and sacral level lesion, respectively, used wheelchairs.

Only two to three percent of children with spina bifida achieve urinary continence and spontaneous voiding without urologic intervention. However 70% of patients can achieve urinary continence with conservative medical therapy. This generally entails intermittent catheterization rather than spontaneous voiding to empty the bladder, medications to improve bladder capacity and compliance, and in approximately one-quarter of patients, surgical intervention.[8]

Numerous studies have documented that children with spina bifida are at increased risk for a variety of neuropsychological and behavioral problems. These include impairments in cognitive, perceptual-motor, memory, fine and gross motor, language, and attention skills, as well as academic achievement and psychosocial functioning. Intelligence quotients (IQ) of children who have myelomeningocele and a common complication, hydrocephalus, vary widely but tend to cluster in the borderline to low average range, i.e., IQ's of 70-90. Difficulties with memory and attention are also frequently reported, particularly in children with hydrocephalus.[9,10] Given the multiple areas of cognitive function that may be affected, it is not surprising that academic performance is often adversely impacted. Children with spina bifida are also at risk for poorer psychosocial adjustment in relation to the general population.[11] More specifically, children with spina bifida have been found to have higher rates of internalizing and externalizing behavior problems than unaffected children based on parental reports.[11]

2.3 RATIONALE FOR PRENATAL REPAIR OF MYELOMENINGOCELE

In a fetus with myelomeningocele, there is evidence that neurologic function deteriorates during gestation. First, sonographic evaluation suggests that both the central and peripheral nervous system insults may be progressive. The Chiari malformation and ventriculomegaly are often seen to progress during fetal development. Lower extremity movement can be seen early in gestation (before seventeen to twenty weeks) and is not seen later. Clubbing of the feet associated with myelomeningocele also appears to be progressive throughout gestation. Secondly, experimental and clinical work in other areas of nervous system development suggest that plasticity is greatest in the young brain and nervous system.[12] Recovery of function after CNS damage from traumatic and hypoxic insults is better in neonatal animals than it is in adult animals. In summary, if the myelomeningocele can be safely repaired in utero, relatively early in gestation, it is plausible that neurologic function could be substantially improved.

2.4 ANIMAL STUDIES

Animal studies have demonstrated that prenatal coverage of the lesion may preserve neurological function. Michejda created a spina bifida-like lesion in eight Macaca mulatta fetuses by performing intrauterine lumbar laminectomy and displacing the spinal cord from the central canal.[13] This condition was repaired in utero in five monkeys. At delivery, the five animals whose lesion was covered developed normally, while those with open lesions were

paraplegic with lower extremity somatosensory loss and incontinence. Studies performed in the rat model showed that those animals in which the defect remained uncovered were born with a severe deformity and weakness of the hind limbs and tail.[14] In contrast, repaired rats were normal at birth. Histological studies of the exposed spinal cord revealed findings similar to those described in children with myelomeningocele. Similar studies have been performed in fetal pigs and lambs with identical results.[15,16,17] It has recently been shown in an open spinal canal fetal lamb model that hindbrain herniation can be prevented by mid-gestational repair of the surgically created myelomeningocele.[18] It is now hypothesized that the neurological defects seen in children with myelomeningocele result from both the congenital myelodysplasia as well as from intrauterine spinal cord injury resulting from prolonged exposure of neural elements to the intrauterine environment.

2.5 CLINICAL STUDIES

Starting in 1994, the first cases of myelomeningocele repair in utero were performed using a fetoscopic approach. This approach did not result in satisfactory repair of the lesion and was abandoned quite quickly. In 1997, the first cases were carried out by hysterotomy. As of April 1, 2002, 212 women had received open fetal repair of myelomeningocele at three centers: University of California San Francisco (UCSF), Children's Hospital of Philadelphia (CHOP), and Vanderbilt University Medical Center.

TABLE 1: FETAL REPAIR OF MMC (OPEN REPAIR ONLY) BY YEAR OF SURGERY AS OF 04/01/2002

YEAR	CHOP	VANDERBILT	UCSF
1997	0	3	0
1998	4	26	1
1999	9	45	1
2000	18	39	6
2001	15	30	2
2002	3	9	1
TOTAL	**49**	**152**	**11**

The CHOP cases include two fetal and one neonatal death. At Vanderbilt, there were two fetal deaths, two neonatal deaths, and one infant death at ten months of age. In addition, one child died at three years of age due to complications of ventriculostomy (not included in the table). At UCSF, there was one fetal death and two deaths from complications of prematurity. The current ages of the surviving infants are as follows:

TABLE 2: CURRENT AGE OF INFANTS/STATUS OF PREGNANCIES WITH OPEN FETAL REPAIR OF MMC AS OF 04/01/2002

	CHOP	VANDERBILT	UCSF
Died	3	5	3
Not born yet	2	7	1
< 12 months	15	28	1
12 - < 24 months	17	40	5
24 - < 36 months	8	44	1
36+ months	4	28	0
Total	**49**	**152**	**11**

2.5.1 SHUNT-DEPENDENT HYDROCEPHALUS

The table below describes the experience at the three centers for the fetal surgery patients who reached one year of age as of April 2002. As a comparison, at CHOP, of 416 patients followed in the Spina Bifida Clinic, 84% had a shunt by one year of age. The distribution of lesion levels among the fetal surgery patients was similar to these clinic patients.

TABLE 3: 1 YEAR SHUNT RATES FOR SURVIVING FETAL SURGERY PATIENTS

	CHOP	VANDERBILT	UCSF
Shunt by 12 mos	13	61	3
No shunt by 12 mos	16	50	3
Missing outcome	0	1	0
Total	**29**	**112**	**6**
Shunt rate	44.8%	55.4%	50.0%

Although the shunt rates differ somewhat between the centers, this may be explained by differences in gestational age at repair, which, like lesion level, was shown in the Vanderbilt series to be associated with the hydrocephalus outcome. All of the repairs at CHOP were performed early in gestation, at 21-24 weeks. At Vanderbilt, 25/58 fetuses (43.1%) of surviving fetuses repaired at less than 25 weeks compared with 37/54 (68.5%) of those repaired later required a shunt.

2.5.2 HINDBRAIN HERNIATION

Investigators at Vanderbilt compared the postnatal MRIs of 26 of their original 28 patients who underwent in utero surgery with MRIs or ultrasounds in 22 historical controls. They found the following results:[19]

TABLE 4: HINDBRAIN HERNIATION IN FETAL SURGERY PATIENTS AND CONTROLS AT VANDERBILT

GRADE	0-1	2-3	4-5
Fetal Surgery	17	9	0
Control	1	18	3

Using a different grading scale, the CHOP group similarly demonstrated a marked improvement in the degree of hindbrain herniation following in utero repair. All nine of the patients had scored a grade 3 on MRIs done between weeks 19 and 24 gestation. MRIs done three weeks after fetal closure of myelomeningocele showed improvement in all nine and, on the MRI obtained six weeks postnatally, all nine were Grade 1 (normal).[20] This result has subsequently been confirmed in that every single delivered patient at CHOP by August 2001 (36 excluding deaths) has demonstrated improvement in hindbrain herniation.

2.5.3 LEG FUNCTION

An analysis of the leg function of the first 26 patients to undergo in utero repair of myelomeningocele at Vanderbilt revealed no significant difference from a set of historical controls who were treated in the conventional fashion (postnatal repair).[19] The average anatomic level in the prenatal surgery group was L5 while that in the control group was L2/L3. However, the neurologic level in the prenatal surgery group was L4/L5 while that in the control group was L2/L3. Thus as a group, the upper anatomic level of the lesion closely

matched the neurological level. The average age at the time of this neurological examination was approximately six months. All intrauterine repairs were performed at more than 25 weeks' gestation.

In 34 patients with in utero repair at CHOP, several had neurological function substantially better than might have been expected after conventional repair. Fifteen of 34 patients evaluated as newborns had lower extremity function better than expected by at least two spinal levels based on anatomic level as determined by the initial MRI. Interestingly, all of these patients were operated on at less than 25 weeks gestation, suggesting that earlier repair of the myelomeningocele may result in improved lower extremity function.

A follow-up on 30 infants from Vanderbilt who have reached age two and for whom data are available, indicates that 80% were ambulatory (15 were 'cruising', 3 walking with long leg braces, 1 with ankle orthotics and 5 unaided).

These results suggest that in utero surgery does not worsen and may improve leg function in infants so treated. Other issues, such as an improved ability to detect pain and temperature, could clearly improve quality of life even in the absence of normal motor function by allowing the individual, for example, to prevent burns or avoid pressure sores.

2.5.4 BOWEL AND BLADDER FUNCTION

The effect of fetal myelomeningocele repair on urologic function remains largely unknown at this time. In a preliminary study of 26 patients who had undergone fetal myelomeningocele repair at Vanderbilt, no significant improvement in urologic function could be appreciated as compared with patients treated in the conventional fashion.[19] However, the population had an average age of six months, and urologic testing is relatively unreliable at this age. An update on those from Vanderbilt who reached two years by August 2001 (30 patients with available data), revealed that all were 'socially continent' of bladder and bowel, although 37% were catheterized, 73% had been treated for a bladder infection and 57% demonstrated typical management of bowel symptoms (on oral medications, altered diet, requiring assistance with evacuation).

2.5.5 COGNITIVE FUNCTION

Of the 19 infants who had reached one year of age by August 2001 at CHOP, eleven returned for a developmental assessment. The Bayley Scales of Infant Development and the Preschool Language Scales (PLS) were conducted. The mean MDI was 86 and PDI was 56. The mean total PLS was 85. All three scores have a standardization mean of 100, and standard deviation of 15. Overall, two of the children were demonstrating a significant global delay.

Developmental data were collected and reported on the first group of 26 infants aged 2 to 18 months who underwent fetal surgery at Vanderbilt.[21] Their average MDI was 100, with a range from 80 to 118. More recent data are not available, since the quality of the Bayley data collected from the many different clinics was felt to be too variable.

2.6 POTENTIAL RISKS OF FETAL SURGERY

2.6.1 MATERNAL RISKS

Not only does the fetus face the potential risks of the intrauterine surgery, but also the mother's health may be threatened without the possibility of any direct benefit. She undergoes two laboratory incisions during the index pregnancy, one at the time of fetal surgery and the other with cesarean delivery at birth. Thus, she is at risk for the standard operative morbidities incurred by any major abdominal surgery including: bleeding, perhaps requiring transfusion; wound infection or breakdown; uterine infection; damage to adjacent organs such as the bowel or bladder; immediate damage to the uterus requiring hysterectomy; pulmonary edema in the immediate postoperative period; allergic reactions to medications; and even death. Pulmonary edema in the immediate postoperative period has occurred in approximately 8% of the patients in the Vanderbilt series and has responded promptly to medical management. None required intubation or admission to the ICU. In the combined experience at UCSF, CHOP and Vanderbilt with over 200 open fetal surgeries for a variety of fetal diseases, there have been no intra-operative maternal complications or maternal deaths.[22,23] In one instance at Vanderbilt, the mother abrupted during surgery, requiring intraoperative delivery of the 28-week fetus who survived. If this were to occur prior to 24 weeks' gestation, it would be unlikely that the baby would survive.

Due to the extent and type of uterine surgery required for access to the fetus for open repair, the mother is at increased risk of uterine rupture during that pregnancy and with all subsequent deliveries. The mother is also at risk for significant adhesions resulting in difficulty in performance of the cesarean section, development of bowel obstruction and postoperative pain. As with any previous uterine surgery, there can be abnormal implantation of a placenta in a subsequent pregnancy over the scar from the hysterotomy, resulting in a placenta accreta or placenta percreta.

In the Vanderbilt series, no catastrophic uterine ruptures have occurred, although in one case the fetal foot extruded through the incision at about 34 weeks requiring urgent delivery and uterine repair with good maternal and fetal outcomes.

A study of 45 women who underwent open fetal surgery at UCSF for a variety of indications over a 15-year period was recently published.[24] There were 35 attempted pregnancies. Thirty-two were successful resulting in 31 live births. Of the three that have not conceived, two had a strong history of infertility, and one had only been trying for three months. This suggests that even open hysterotomy, fetal manipulation, and suture closure of the hysterotomy has a minimal impact on maternal fertility.

Finally, there are potential psychological risks such as the mother feeling "coerced" into having prenatal surgery performed. There are few mothers who will not do "everything" for their child(ren). It is critical that the perioperative counseling for these women and their partners/families legitimize and give "permission" to the woman to decide against surgery, or in this case, the randomized trial. The woman is likely to be on medical leave from work for the duration of her pregnancy and, as such, there is potential for financial harm as well as psychosocial complications.

2.6.2 FETAL INTRAOPERATIVE RISKS

The fetus also undergoes intraoperative risks including asphyxia from cord occlusion when the amniotic fluid is drained which is addressed via monitoring of the fetal heart rate during the surgery. Damage to the fetal spinal cord or adjacent structures during the surgery is a risk during any myelomeningocele repair, but may be more likely with intrauterine repair due to the small size of the preterm fetus, and the reduced exposure associated with surgery through a hysterotomy. Infection is a significant risk of any surgical procedure, but carries greater significance in an obstetrical patient in whom chorioamnionitis requires prompt delivery. There is a risk of intrauterine infection requiring delivery secondary to premature labor and oligohydramnios. Intrauterine infection requiring preterm delivery has been reported twice in the Vanderbilt series. Oligohydramnios of uncertain etiology has occurred at least transiently in about one third of the patients in the Vanderbilt series although only one significant neonatal problem has been noted. One fetus developed pulmonary hypoplasia secondary to longstanding oligohydramnios and died shortly after delivery.

2.6.3 PRETERM BIRTH

Preterm labor remains an unsolved problem. Avoiding a long hysterotomy by operating earlier in gestation may decrease the incidence of preterm labor by decreasing uterine injury. Nevertheless, the fetus is at increased risk of premature birth and its sequelae including sepsis, intraventricular hemorrhage, respiratory distress syndrome, necrotizing enterocolitis and death. In August 2001, the average gestational age at delivery was 33.9 weeks at CHOP, 33.7 at Vanderbilt and 32.5 at UCSF. It should be noted that many of the 34-37 week deliveries were planned cesarean births after documentation of pulmonary maturity in order to preempt the risk of uterine rupture in the last few weeks of pregnancy. The neonate's risks of prematurity complications after 34 weeks are fairly minimal.

2.7 RATIONALE FOR THE CLINICAL TRIAL

Enthusiasm for fetal intervention must be tempered by reverence for the interests of the mother and her family, by careful study of the disease in experimental fetal animals and untreated human fetuses, and by a willingness to abandon therapy that does not prove effective and safe in properly controlled trials.

To date, clinical results of fetal surgery for myelomeningocele are based on comparisons with historical controls and address efficacy rather than safety. Historical controls are problematic due to constantly improving postnatal management and the problem of ascertainment bias. For example, parents may cause distortion of outcome assessment by avoiding postnatal shunting. Only a properly designed and conducted randomized trial will be sufficient to overcome bias.

Some have argued that randomization of treatment for such an emotionally charged disease is difficult and will not be accepted by families.25 However, a randomized, controlled trial of fetal surgery for diaphragmatic hernia sponsored by the NIH has enjoyed better than expected enrollment. Many families are relieved, once they know that the best treatment is truly unknown, to have the choice taken out of their hands. A randomized trial for myelomeningocele is clearly difficult but it must be done to determine whether fetal repair of myelomeningocele, with its attendant maternal and neonatal morbidity, is warranted. It is important to launch a trial before more centers begin doing the procedure.

3 STUDY DESIGN

3.1 PRIMARY RESEARCH QUESTIONS

1. Does intrauterine repair of fetal myelomeningocele at 19^0 to 25^6 weeks gestation using a standard multi-layer closure improve outcome, as measured by death or the need for ventricular decompressive shunting by one year of life, compared with standard postnatal repair?

2. Does intrauterine repair of myelomeningocele improve neurologic function at 30 months corrected age as measured by a combined rank score of the Bayley Scales of Infant Development mental development index and the difference between the motor level and lesion level?

3.2 SECONDARY RESEARCH QUESTIONS

Secondary research questions this study will address include:

- Does intrauterine repair of myelomeningocele improve the degree of the Chiari II malformation as measured by magnetic resonance imaging (MRI)?

- Does intrauterine repair of myelomeningocele improve the postnatal course and neurologic outcome of the infant? Neurologic function will be assessed by detailed neuromotor function analysis, cognitive testing, and evaluation of neurodevelopmental status at twelve and thirty months of age.

- What are the long-term psychological and reproductive consequences for the parents?

3.3 DESIGN SUMMARY

The study is an unblinded randomized controlled clinical trial of 200 patients. Patients diagnosed with myelomeningocele at 16 to 25 weeks gestation will be referred to the Data and Study Coordinating Center (DSCC) for initial screening and information. Those eligible and interested will be assigned by the DSCC to a Fetal Surgery Unit (MOMS Center) where final evaluation and screening will be carried out. Patients who satisfy the eligibility criteria and consent to randomization will be centrally randomized to one of the following two management protocols:

- Intrauterine repair of the myelomeningocele at 19^0 to 25^6 weeks, discharge to nearby accommodation on tocolytics when stable for preterm labor, weekly prenatal visits and monthly ultrasounds conducted at the MOMS Center; cesarean delivery at 37 weeks following demonstration of lung maturity.
- Return to local perinatologist for prenatal care, with monthly ultrasounds reported to the MOMS Center; return to the MOMS Center at 37 weeks gestation for cesarean delivery following demonstration of lung maturity; neonatal repair of the myelomeningocele.

3.4 ELIGIBILITY CRITERIA

3.4.1 INCLUSION CRITERIA

1. Myelomeningocele (including myeloschisis) at level T1 through S1 with hindbrain herniation. Lesion level will be confirmed by ultrasound and hindbrain herniation will be confirmed by MRI at the MOMS Center.
2. Maternal age ≥ 18 years
3. Gestational age at randomization of 19^0 to 25^6 weeks gestation as determined by clinical information and evaluation of first ultrasound. If the patient's last menstrual period 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 ± 10 days, 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 26-32 day window or if the measurements from her first ultrasound are more than 10 days discrepant from the ultrasound), the ultrasound determination will be used. Once the EDC has been determined for the purposes of the trial, no further revision is made.
4. Normal karyotype with written confirmation of culture results. Results by fluorescence in situ hybridization (FISH) will be acceptable if the patient is at 24 weeks or more.

3.4.2 EXCLUSION CRITERIA

1. Non-resident of the United States
2. Multifetal pregnancy
3. Insulin dependent pregestational diabetes
4. Fetal anomaly not related to myelomeningocele. A fetal echocardiogram will be conducted before randomization and if the finding is abnormal, the patient will be excluded.
5. Kyphosis in the fetus of 30 degrees or more
6. Current or planned cerclage or documented history of incompetent cervix
7. Placenta previa
8. Short cervix < 20mm measured by ultrasound. The patient may be excluded based on an ultrasound report during initial screening or based on the cervical length measurement performed at the MOMS center as part of the final evaluation.
9. Obesity as defined by body mass index of 35 or greater
10. Previous spontaneous singleton delivery prior to 37 weeks

11. Maternal-fetal Rh isoimmunization, Kell sensitization or a history of neonatal alloimmune thrombocytopenia

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

13. Known Hepatitis-C positivity. If the patient's Hepatitis C status is unknown, she does not need to be screened.

14. Uterine anomaly such as large or multiple fibroids or mullerian duct abnormality.

15. Other maternal medical condition which is a contraindication to surgery or general anesthesia.

16. Patient does not have a support person (e.g., husband, partner, mother).

17. Inability to comply with the travel and follow-up requirements of the trial.

18. Patient does not meet other psychosocial criteria (as determined by the psychosocial interviewer using a standardized assessment) to handle the implications of surgery.

3.5 INFORMED CONSENT CRITERIA

Written consent will be obtained from patients after their initial contact with the DSCC to permit further contact and review of their medical records. The consent form is included in Appendix B.1 'Consent Form for Screening'. Upon arrival at a participating MOMS Center, the pregnant woman (and her partner) will be informed about the entire process of counseling and evaluations. The actual steps leading up to randomization will be discussed, and consent to undergo the evaluations will be signed by the patient. The reasons for randomized controlled trials, and the necessary elements for a well-conducted trial as well as the particular requirements for this trial will be discussed. Also, the patients will be told that they can, at any time, decline continued participation in the evaluation or the trial. Full disclosure of the nature and potential risks of participating in the trial will be made. A common consent form is included in Appendix B.2 The patient will also be asked to sign a consent form for follow-up of her infant as part of the study. A common consent form for this part of the trial is included in Appendix B.3 Minor modifications will be made to these consent forms at each center as necessitated by the requirements of each individual institutional review board.

Women who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent will be obtained in that language; if this is not possible the patient will not be included. She will also be asked to sign a release for her medical records. Following the guidelines of the local IRB, the father's consent will also be obtained.

3.6 RANDOMIZATION METHOD AND MASKING

Randomization assignment will be based on a randomization sequence prepared using the simple urn model, stratified by center, and maintained centrally by the DSCC.[26] The advantage of the urn model is that it provides a good probability of balance, and future assignments are unpredictable, in addition to allowing an explicit randomization analysis to be conducted with relative ease. Stratification by center assures balance between the two treatment groups with respected to possible differences in patient management. Because this is an unmasked trial, central randomization via a secure Internet procedure will be used.

Although the trial is unmasked, independent consultants who will be blinded to the infant's randomization group will perform primary outcome assessment.

4 STUDY PROCEDURES

4.1 PRE SCREENING FOR ELIGIBILITY

Patients from the United States with prenatally diagnosed fetal spina bifida who are interested in trial participation will contact the DSCC. Publicity about the study will be coordinated by the DSSC, and will be directed to patients, physicians and other health care providers.

If a patient appears to meet minimal eligibility criteria, basic rules for participation in the trial will be discussed with the patient. To minimize noncompliance and loss to follow-up, patients who appear unwilling to accept any portion of the trial, including randomization to either group, and delivery and follow-up at the assigned MOMS Center, will not be considered eligible for trial participation.

For patients who remain interested in trial participation, eligibility will be verified and the patient will also be asked to make arrangements for an amniocentesis for karyotyping. A standardized packet of information will then be mailed to the patient, containing material describing spina bifida, including prenatal and neonatal development, general outcomes expected, and management options in pregnancy and the newborn period. The packet will also contain information describing the study, including the rationale and general study design.

4.2 ASSIGNMENT TO MOMS CENTER

If the patient remains eligible and interested, she will be directed to one of the three participating centers. To eliminate selection bias, patients will be assigned to a MOMS Center based on geography to ensure that each center is assigned equal numbers of patients. The number of patients assigned to each MOMS Center will be monitored quarterly by the DSCC, and if necessary the patient distribution will be shifted to ensure equal numbers of patients at each center. Patients must agree to the assignment of MOMS center or they will not be enrolled in the study.

4.3 FINAL SCREENING

Once the patient is referred to a participating MOMS Center, she will contact that site for intake. The study coordinator will assist the patient and her family in obtaining suitable transportation and lodging for the scheduled evaluation. Patient evaluation for study participation will consist of the following procedures.

1. Comprehensive obstetrical ultrasound examination, including documentation of cervical length, fetal gestational age, lesion level, ventricular size, leg and foot positioning, and lower extremity movement, in addition to a fetal echocardiogram.
2. Fetal MRI to document hindbrain herniation.
3. Maternal physical examination and clearance for surgery by anesthesia and the OB/GYN staff.

4. Psychosocial evaluation to identify family dynamics and social issues that will impact the family's strategies for the remainder of the pregnancy and after the birth of the child. The social worker will also develop interventions if such issues are identified.

5. Teaching about neural tube defects, community resources, information regarding prenatal and postnatal surgery, management following prenatal surgery, and recommendations for continued care for the postnatal group.

6. An ethics focused interview to afford potential participants a formal opportunity to examine what they have learned about the study in the course of their evaluation and to discuss how they feel about enrolling in the study.

4.4 INFORMED CONSENT

When it has been determined that the patient meets all of the inclusion criteria and has none of the exclusion criteria, and the patient indicates a willingness to undergo randomization (i.e., will accept either pre- or post-natal surgery), she will be asked to sign both the informed consent form for the study and for follow-up.

4.5 PSYCHOLOGICAL TESTING

Once the patient has given consent but prior to randomization, she and her partner will be asked to complete the psychosocial questionnaires listed below. These are administered prior to randomization so that surgery group assignment will not affect the baseline results. The data from these questionnaires will provide indications for the parents' emotional functioning, subjective well-being, subjective opinion of met and unmet needs, levels of optimism/pessimism and stress.

1. Satisfaction with Life Scale (SWLS) - The SWLS measures life satisfaction as a cognitive-judgmental process, using a seven-point Likert scale. This scale has high test-retest reliability with correlation coefficients of 0.54 to 0.80.[27] Pavot compared the SWLS to other related scales and found it was valid and reliable and could be used in a variety of age groups and applications.[28]

2. Life Orientation Test (LOT) - The LOT is an eight item instrument measuring "dispositional optimism", the degree to which individuals expect favorable outcomes, rated on a five point Likert scale. The LOT includes items such as "every cloud has a silver lining", wherein such optimistic slogans are endorsed or denied. According to Scheier and Carver, the LOT has a Cronbach's alpha of 0.76 and a reliability coefficient of 0.79.[29]

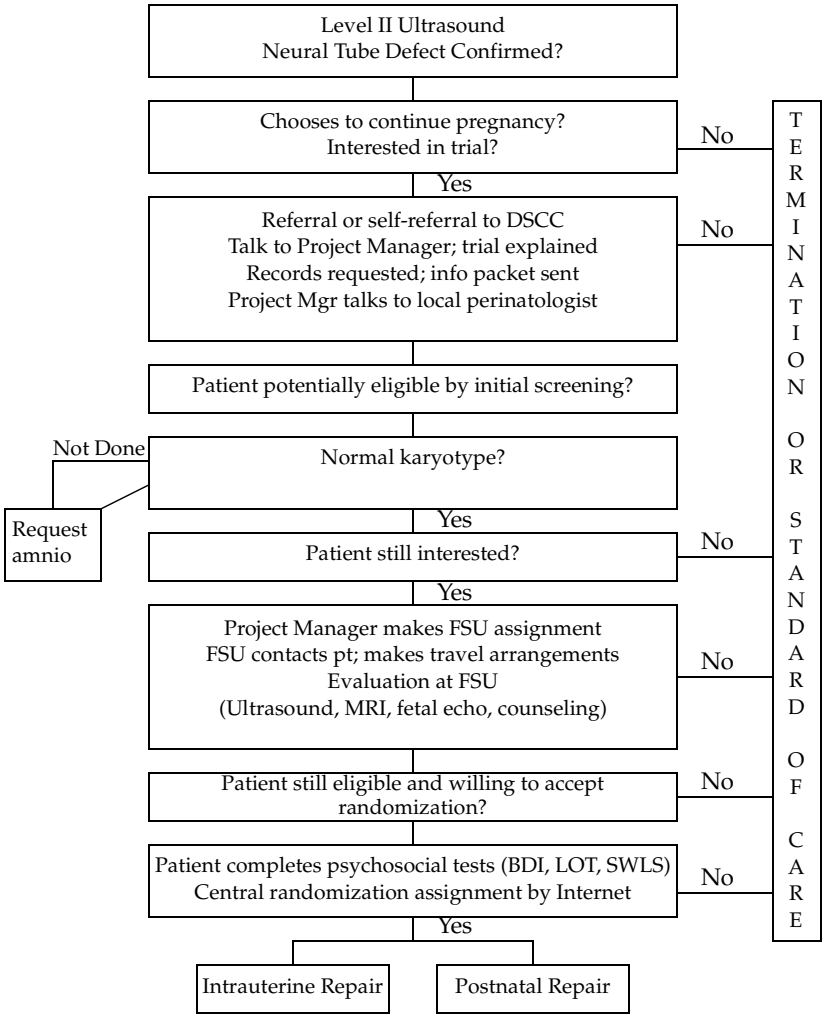
3. Beck Depression Inventory (BDI) - The BDI is a widely used 21-item self report measure of depressive symptoms which has been shown to be a reliable and valid measure of severity of depressive symptomatology in clinical populations.[30] Internal consistency ranges from 0.73 to 0.92, with a mean of 0.86 and has a reliability coefficient of 0.93.[31] The BDI takes approximately 10 minutes to complete and requires a fifth to sixth grade reading level. The BDI has been translated into several languages, including Spanish, and the reliability and validity of these translated versions has been verified.

4.6 RANDOMIZATION

The randomization assignment will then be obtained via the central Internet randomization system. Patients assigned to the fetal surgery group will be scheduled for surgery no less than one working day later and no more than three working days or 25^6 weeks gestation, whichever is earlier.

Screening and randomization procedures are summarized in the figure below.

FIGURE 1. SCREENING AND ENROLLMENT



4.7 PATIENT MANAGEMENT AND FOLLOW-UP

4.7.1 PRENATAL SURGERY GROUP

Patients randomized to the prenatal surgery group will be scheduled for surgery no sooner than the following working day, and no later than three working days after randomization or 25^6 weeks gestation, whichever is sooner. Patients will undergo open fetal surgical repair of

the myelomeningocele with standardized intraoperative techniques, post-operative care and cesarean delivery performed by each of the three fetal surgery teams (including the surgeons, perinatologists and neurosurgeons). A description of the surgery is presented in Appendix C. All surgeries will be performed by open hysterotomy since the previous experience with the endoscopic approach was unsatisfactory.

Since prenatal surgery patients are at increased risk of preterm labor, use of tocolytics is planned until 36^6 weeks gestation. All patients will stay in the hospital until they are on a regular diet, have return of bowel function, are able to ambulate to the bathroom without assistance, demonstrate good tocolytic control, and have good postoperative pain management on oral medications. All discharged patients (and their support person) will stay close to the MOMS Center in accommodations provided to permit standardized postoperative management, ultrasound evaluation, and delivery. They will be on modified bedrest for the first two weeks, but subsequently allowed to graduate to moderate activity if the uterus is quiescent.

Outpatient follow-up will be scheduled every week. In addition to the usual content of a prenatal visit, maternal assessment will include the degree of postoperative discomfort, wound healing, and premature labor/delivery risks. A brief "targeted" ultrasound will be performed to assess amniotic fluid volume and membrane status since oligohydramnios and chorioamniotic separation are the most frequent complications following fetal surgery and their presence may directly impact pregnancy management. Fetal well-being will be determined at every visit after 28 weeks by means of a biophysical profile.

Comprehensive ultrasonography will be performed monthly to measure: biparietal diameter, head circumference, femur length, humerus length, abdominal circumference, amniotic fluid index and maximum vertical pocket, status of the chorion, diameter of the posterior horn of the lateral ventricles, lateral ventricular width/hemispheric width ratio, and appearance of the third ventricle.

If staying near the MOMS Center becomes a cause for considerable hardship for a patient and if she is cleared for travel, she may return home. Before her departure, the team perinatologist or Principal Investigator will contact the local perinatologist directly to facilitate a smooth transfer of patient information and follow-up plans, and to ensure that patient management guidelines are clear, as outlined in a standardized letter which will be sent at the same time. This will include ultrasound specifications. The monthly ultrasound examinations on videotape will be forwarded by express mail, (or transferred by internet if the technology is available at the local center) to the MOMS Center, as well as prenatal records. Upon reaching 32^0 weeks gestation undelivered, and if she is cleared to travel, including to fly if applicable, the patient and her support person will return to the participating MOMS Center for elective cesarean delivery at 37 weeks, given fetal lung maturity.

4.7.1.1 USE OF ANTENATAL STEROIDS

Steroids will not be used at the time of antenatal surgery, but only in the case of threatened preterm delivery prior to 34 weeks. If preterm labor is diagnosed and the likelihood of delivery is high (e.g., there is premature membrane rupture, vaginal bleeding, or nonreassuring antepartum fetal surveillance), a course of steroid therapy will be given to

minimize any complications of prematurity. The steroid course is two doses of 12 milligrams of betamethasone 24 hours apart, and will be given once between 24 weeks and 34 weeks of gestation. This regimen was developed for the prenatal surgery group, but would also apply to patients in the postnatal group who present with threatened preterm delivery.

4.7.1.2 USE OF TOCOLYTICS

Magnesium sulfate will be started postoperatively in the operating room and will be continued for the first 24 to 48 hours following surgery. Indomethacin will be given as a 50 mg suppository preoperatively, followed by 50 mg (p.r. or p.o.) every 6 hours for the first 24 hours following surgery and 25 mg every 6 hours on the second day. During the time that the mother is on indomethacin, two fetal echocardiograms will be conducted. Maintenance therapy will consist of p.o. nifedipine (10-20 mg every 4-6 hours) and will be continued until 36 weeks 6 days. If nifedipine fails, i.e. the patient experiences more than eight contractions per hour, or if it is not tolerated, a terbutaline pump will be used.

First line tocolysis will be re-initiated for fetal surgery patients or initiated for patients assigned to postnatal surgery when there have been palpable, uncomfortable contractions occurring preterm for longer than one hour, and at a frequency of greater than or equal to 4 per 20 minutes. Magnesium sulfate will remain the primary tocolytic in such cases.

4.7.1.3 MANAGEMENT OF OLIGOHYDRAMNIOS AND INTRAUTERINE GROWTH RESTRICTION

Oligohydramnios will be managed by bed-rest with bathroom privileges when the AFI is less than the 5th percentile and, for in-hospital management, with fetal heart rate or NST assessment every nursing shift when the AFI is less than the 2.5th percentile. The only indication for amnioinfusion will be severe oligohydramnios with evidence of cord compression. Written guidelines will be developed and also provided to the community physicians who may be involved in monitoring these patients. Intrauterine growth retardation (IUGR) is defined as a fall off in fetal size and weight to less than the 10th percentile by ultrasound biometry. This has occurred only rarely in fetal surgery patients and would be managed as any other pregnancy complicated by IUGR (bed rest, maternal nutrition, frequent fetal surveillance, and umbilical artery Doppler velocimetry).

4.7.1.4 MANAGEMENT OF FETAL DISTRESS

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

4.7.1.5 MEMBRANE SEPARATION

When membrane separation is seen by ultrasound, patients will be placed on bed rest with bathroom privileges only. If the membrane separation progresses and extends to the placental cord insertion site, patients will be admitted to the antepartum service on bed rest, and a fetal heart rate strip will be collected every shift and if decreased fetal movement is observed.

4.7.2 DELIVERY

Upon documentation of fetal lung maturity at 37^0 weeks gestation, delivery will occur via cesarean section. If fetal lung maturity is not demonstrated, delivery will be delayed five to seven days. Delivery by cesarean section is necessitated by the presence of the fundal hysterotomy scar. If the patient experiences preterm labor at less than 34^0 weeks gestation unresponsive to tocolytic therapy, rupture of membranes at less than 34^0 weeks gestation, chorioamnionitis, suspected uterine rupture, placental abruption or a non-reassuring fetal status, she will be delivered via cesarean section.

Although the same abdominal incision will usually be used for the cesarean section as for the prenatal surgery, the fetus is preferably delivered via a lower uterine segment incision. The uterine and abdominal incisions will be closed in routine fashion. A full description of the hysterotomy site will be recorded.

Babies will be stabilized and routine neonatal evaluation will be performed. If the fetal repair of the myelomeningocele was unsuccessful, standard postnatal operative repair of the myelomeningocele will be performed as soon as the baby is stable, usually within 48 hours of delivery, by the MOMS Center surgical team.

4.7.3 POSTNATAL SURGERY GROUP

Patients randomized to the postnatal surgery group will return to their community of origin for prenatal care under the direct supervision of a perinatologist. The team perinatologist or PI will contact the local perinatologist directly to facilitate a smooth transfer of patient information and follow-up plans. A standardized letter will be sent to the local perinatologist detailing the patient management guidelines. Obstetrical ultrasonography will be obtained monthly at the closest prenatal diagnosis center. All prenatal records, and ultrasound tapes will be regularly forwarded to the participating MOMS Center where the patient was randomized, as outlined above.

At 37^0 weeks, if the patient is undelivered, the woman and her support person will return to the participating MOMS Center for delivery. Once at the center, the MOMS Center team perinatologist will perform an amniocentesis for pulmonary maturity studies, if necessary. Demonstration of fetal lung maturity may be made by appropriate interpretation of LS, FLM, TDX, or PG. If fetal lung maturity is not demonstrated, delivery will be delayed by 5 to 7 days. If the amniocentesis results indicate a low risk of pulmonary immaturity, or if performance of an amniocentesis is not technically possible, she will be assessed preoperatively, and cesarean birth will be performed. Patients will be delivered operatively because of evidence suggesting that children with myelomeningocele have increased neurologic deficits if not delivered by cesarean section.[32,33]

If the patient experiences preterm labor before 37^0 weeks gestation unresponsive to tocolytic therapy, rupture of membranes before 37^0 weeks gestation, chorioamnionitis, suspected uterine rupture, placental abruption or a nonreassuring fetal status, she will be delivered at her community of origin via cesarean section.

Postnatal repair of the myelomeningocele is not an emergency procedure. Babies will be stabilized and routine neonatal evaluation will be performed. Standard postnatal operative

repair of the myelomeningocele will be performed when the baby is stable by the same MOMS Center surgical team that completes the prenatal repairs. Infants with myelomeningocele usually have a one- to two-week hospitalization during which time growth and development as well as the development of hydrocephalus is monitored and baseline assessments of the genitourinary and musculoskeletal systems are performed.

4.8 ADVERSE EVENT REPORTING

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol. The NICHD Program Scientist will be notified immediately by telephone of any maternal, fetal or neonatal deaths. An Adverse Event Report Form will be sent by fax within twenty four hours to the DSCC and the NICHD. If the patient is in the fetal surgery group, a copy should also be forwarded to the appropriate local Oversight Committee. A copy of the patient's medical record should be made and sent to the DSCC.

Any event that is serious and/or unexpected in nature, severity, or frequency will also be reported promptly by completing an Adverse Event Report Form to be sent to both the NICHD and the DSCC. A copy of the patient's medical record will be made, as the DSCC may request this at a later date for review by the Data and Safety Monitoring Committee (DSMC).

The DSMC will review all Adverse Event Report Forms and other interim safety data and will provide a report to the principal investigators, to the local Oversight Committees and to the IRBs.

4.9 NEONATAL MAGNETIC RESONANCE IMAGING AND ULTRASOUND

MRI of the head and the spine, and an ultrasound of the head will be obtained before discharge. The MRI films and ultrasounds will be forwarded to the DSCC for blinded central review by an independent committee of radiologists. (the Radiology Review Committee).

4.10 PSYCHOLOGICAL TESTING

All mothers will be asked to complete the SWLS, LOT, and BDI within one month of delivery. For those women randomized to the postnatal surgery group, the psychosocial assessments should be obtained after surgical repair of the myelomeningocele. For those mothers not delivering at the participating MOMS Centers, the questionnaires will be mailed to their homes for completion. If the BDI indicates that the mother is depressed, she will be referred to a mental health professional.

4.11 INFANT NEUROSURGICAL MANAGEMENT

For all patients delivered at the assigned MOMS Center, postnatal management of the neonate will be provided by the neonatologists at the MOMS Center and by the neurosurgeon of the multidisciplinary MOMS Center team. For patients who deliver at their community of origin, postnatal neurosurgical management will be conducted in consultation with the MOMS Center team neurosurgeon. This will include a request for an MRI to be done at neonatal discharge. The team neurosurgeon will contact the local neurosurgeon directly to facilitate smooth transfer of patient information, management guidelines and follow-up

plans. All neonatal and infant records will be regularly forwarded to the assigned MOMS Center.

When the infant is discharged from the MOMS Center, postnatal neurosurgical management for the first year of life will be conducted in consultation with the MOMS Center team neurosurgeon. The infant will receive serial physical examinations, measurement of head circumference and ultrasound or CT assessments of hydrocephalus. Most often the need for shunting becomes manifest in the first six weeks of life as indicated by increasing head circumference, bulging fontanelles, and increasing hydrocephalus on serial imaging studies. Strict criteria for shunting will be applied (below). Any decision to shunt made at the home institution will be done in consultation with the team neurosurgeon from the assigned MOMS Center using the established criteria, with the other center neurosurgeons as additional consultants if necessary. It is not feasible to expect patients to return to the MOMS Center if the need for shunting develops, as transportation could significantly delay needed decompression.

4.12 INTERIM INFANT FOLLOW-UP

The study coordinator at each participating MOMS Center will be responsible for maintaining contact with the patient throughout the three-year follow-up period. Successful follow-up depends on continuing and regular interaction of the study coordinator with the patients. For example, telephone calls, reminder notes, cards, arrangements for transportation and regularly scheduled visits all impact on the success of the follow-up.

All patients will be contacted at least every three months by phone and questioned regarding any medical developments that might have occurred over that period of time. A detailed history of neurologic function will be taken including a history of neurological procedures, neurologic signs and symptoms and overall neurologic function. The study coordinator will also obtain a detailed history of urologic function including a history of continence or incontinence, urinary tract infection, need for catheterization, and catheterization schedule as well as information regarding fecal continence or incontinence. Once the infant is of walking age, data regarding ambulation status will be obtained. If infants underwent a Brain Stem Auditory Evoked Response test, swallowing profile, video urodynamic studies, renal sonography and/or an ophthalmologic examination, a copy of the records of these examinations will be forwarded to the participating MOMS Center. Copies of radiographs of the feet, lower extremities, hips and spine will also be forwarded to the participating MOMS Center.

4.13 TWELVE AND THIRTY MONTH FOLLOW-UP VISITS

All patients and their infants will be required to return to the assigned MOMS Center for purposes of follow-up at twelve months chronological age and thirty months corrected age. Outcome Evaluation Teams each comprised of a developmentalist, a psychologist or psychometrist, and DSCC staff, will travel to the participating MOMS Centers to conduct neurologic, muscle strength and developmental examinations. The developmentalist and psychologist will be independent investigators not associated with the MOMS Centers. If a patient and her infant cannot return to her assigned MOMS Center, arrangements will be made for her to either have her follow-up visit at one of the other MOMS Centers or for the Outcome Evaluation Team to go to her home Spina Bifida clinic to conduct the examinations.

To assure standardization, all examiners will receive central training and certification prior to the start of the follow-up examinations. Only examiners who have been centrally certified will conduct the follow-up exams. To retain certification, each examiner will submit a videotape of a study exam annually and the accompanying data forms.

The examiners will be blinded as to which surgery group the patient was randomized to. Thus, the examiners will be instructed to refrain from asking the mother about her pre- or post-natal experiences. In addition, the parents will also be asked to refrain from revealing this information. Both written guidelines and verbal instructions will be provided to the families in advance of the follow-up visits. DSSC personnel will be present to monitor compliance.

The study coordinators will compose summaries of the evaluations, which can then be sent to the families, their physicians, or both. The following procedures will be conducted.

4.13.1 IMAGING

A plane x-ray of the spine and a MRI of the head and spine will be obtained at the one-year follow-up visit. This will be used to determine the anatomic level of the lesion for the primary outcome.

4.13.2 NEUROLOGICAL EXAM

A neurological examination will be conducted at the 12 and 30 months follow-up visits. This will include measurement of tone, deep tendon reflexes, coordination and movement (not including eye movement). The Gross Motor Function Classification System will be conducted at 30 months.[34] The Gross Motor Function Classification System is based on self-initiated movement with particular emphasis on sitting (truncal control) and walking. The primary criterion in the design of the system is that the distinctions in motor function between levels are clinically meaningful. Distinctions between levels of motor function are based on functional limitations, the need for assistive technology including mobility devices and wheeled mobility, and to a much lesser extent quality of movement.

4.13.3 MUSCLE STRENGTH TESTING

At each evaluation, patients will receive the Manual Muscle Test, a standardized test of muscle strength and lower extremity function graded on a 0-5 scale that enables assignment of a specific neurological level to each leg of a patient. Individual muscles or muscle groups are tested at the hip, knee and ankle bilaterally. These can, in turn, be related to radicular level (L1-S1) using a standard form.[35,36] In instances where there is a discrepancy between legs, the more rostral ("worse") level will be used. Additional parameters tested will include range of motion and general tone.

4.13.4 DEVELOPMENTAL TESTING

Psychological/developmental assessments will be conducted on all infants at each study visit. Direct administration of standardized measures to the children will be combined with parent interviews at each level to obtain information about the children's skills and behavior

across multiple domains of development. A summary of the developmental examinations is presented below:

TABLE 5: DEVELOPMENTAL TESTING

	TEST	VISIT
Gross Motor	Mullen Scales of Early Learning Bayley Scales of Infant Development Gross Motor Classification System	**12 and 30 months** **12 and 30 months** **30 months only**
Fine Motor	Mullen Scales of Early Learning Bayley Scales of Infant Development	**12 and 30 months** **12 and 30 months**
Cognitive	Bayley Scales of Infant Development	**12 and 30 months**
Behavior	Behavior Rating Scale of the Bayley Child Behavior Checklist for ages 2-3	**12 and 30 months** **30 months only**
Language	Mullen Scales of Early Learning	**12 and 30 months**

At twelve months and at thirty months corrected age, the Mullen Scales of Early Learning will be conducted. This scale has five subscales: gross motor, visual receptor, fine motor, expressive language and receptive language. The Bayley Scales of Infant Development-II (BSID) has two subscales, the mental scale and the motor scale, and a Behavior Rating Scale, which is completed by the examiner after the mental and motor scales. The mental scale includes an assessment of sensory/perceptual acuities, discriminations and response; acquisition of object constancy; memory, learning and problem solving; and vocalization. It also includes an assessment of the beginning of verbal communication, basis of abstract thinking, habituation and mental mapping. The motor scale includes an assessment of the degree of body control, large muscle coordination, finer manipulatory skills of the hands and fingers, dynamic movement, dynamic praxis, postural imitation and stereognosis. The Bayley Behavior Rating Scale rates the child's test taking behaviors and measures attention/arousal, orientation/engagement, emotional regulation and motor quality. The Child Behavior Checklist will be administered at the 30-month follow-up exam. It provides the parents' ratings of the child's behavior including what concerns the parent most about their child, and the best things about their child.

4.13.5 VIDEO URODYNAMICS AND RENAL SONOGRAPHY

If video urodynamic studies have not been conducted as part of the routine follow-up care at the infant's home Spina Bifida clinic in the previous year, these studies will be completed at the thirty-month follow-up examination for study purposes. This study is routinely performed with video fluoroscopy so that a voiding study can be performed in the same sitting. A specially designed catheter is passed per urethra through which irrigant is carefully infused into the bladder at a slow and steady rate. Pressures are electronically measured as the bladder fills. A similar catheter is placed in the rectum to measure external abdominal pressure, which is subtracted from the bladder measurements to determine the true pressure generated by the native bladder alone. Once full, bladder emptying is assessed both in terms of bladder pressure, urinary flow rate, and the completeness of emptying. Electrical activity in the sphincters is measured as well.

Likewise, if sonography of the urinary tract has not been completed as part of routine follow-up care at the infant's home Spina Bifida clinic in the previous year, it will be completed at the thirty-month follow-up examination for study purposes. Images will be obtained in the

longitudinal and transverse planes. The length of both kidneys will be measured and correlated with established normal size for age. The presence or absence of hydronephrosis and ureteronephrosis will be determined and classified as mild, moderate, or severe and bladder wall thickness will be assessed.

4.14 PARENTAL FOLLOW-UP

Mothers and their partners (fathers) will complete the SWLS, LOT and BDI at the 12 and 30-month follow-up visits and the mothers will be evaluated for reproductive function at the 30-month follow-up visits. If the results of the BDI indicate that the either parent is depressed, he or she will be referred to a mental health professional.

4.15 OUTCOME MEASURES

4.15.1 PRIMARY OUTCOMES

1. Death or the need for ventricular decompressive shunting by one year of life. This composite outcome was chosen to avoid the problem of competing risks, which can be a source of bias.37 This concern arises when the assessment of the desired outcome cannot be made because of the competing risk of another outcome; in this case an infant that dies cannot be assessed for shunt placement. However, by including death as a component, the primary outcome can be evaluated for all patients. This is intuitively reasonable, since if one treatment improves the shunt rate at the expense of an increased death rate, it should not be judged superior. It should be noted that all fetal and neonatal deaths, including terminations, would qualify for this outcome. There is also a potential for assessment bias in the need for shunting. This is avoided by the use of objective criteria for shunting as follows:

1. Cerebral spinal fluid leakage from the myelomeningocele wound
or

2. Bulging at the myelomeningocele wound
or

3. Any two of the following:

- An increase in the greatest occipital-frontal circumference at a rate of greater than one centimeter per week
- An evaluation of the fontanelle as bulging and pulsating or bulging and hard using the following scale: sunken and soft, flat and soft, bulging and soft, bulging and pulsating, and bulging and hard
- Increasing hydrocephalus on two consecutive ultrasounds or CTs determined by increase in ratio of biventricular diameter to biparietal diameter measured at the foramen of Monro

or

4. In infants less than one week old, a fontanelle evaluated as bulging and hard, together with ventriculomegaly and any of apnea, bradycardia or lethargy

or

5. Development of marked syringomyelia by imaging studies. For this criterion, the MOMS Center neurosurgeon should contact the other two neurosurgeons to review the case.

The necessity for a shunt will be assessed using a blinded adjudication process. Copies of medical records and imaging studies for all infants will be sent to the DSCC, which will be responsible for ensuring that the medical records do not reveal the assigned surgery group of the infant. The MRI obtained at the twelve-month visit to the MOMS Center will be included in the medical records to be reviewed. The records of all infants in the trial will be reviewed by two members of the Shunt Outcome Review committee to determine whether they did or did not meet the criteria for shunt placement. If the two members do not agree, the third member of the committee will review the records and the whole committee will adjudicate the case.

2. A composite outcome of two measures:

- Bayley Scales of Infant Development: The outcome score, evaluated at thirty months corrected age, will consist of the Mental Development Index (MDI) or a score of zero for death. Death is included so that the outcome is measurable in all patients. The MDI scores will be ranked and deaths will receive the lowest rank. The Bayley Scales will be administered by independent trained evaluation teams, who will be unaware of the child's assigned surgery group.

- Distal somatosensory function and motorsensory assessment of level of lesion, evaluated in relation to anatomic level. This can be expressed as the difference between the anatomic and the functional level. The plane x-ray obtained at the 12 month visit will be used to determine the anatomic level. These scores will also be ranked and deaths will receive the lowest rank.

The composite outcome consists of the sum of these two ranks.

4.15.2 SECONDARY OUTCOMES

Secondary outcome measures for this study include the following:

4.15.2.1 MATERNAL/PATERNAL

1. Gestational age at delivery
2. Maternal death
3. Oligohydramnios
4. Uterine rupture
5. Maternal and paternal psychosocial status as measured by the SWLS, LOT and BDI at delivery, 12 and 30 months after delivery
6. Maternal reproductive functioning at 30 months post delivery

4.15.2.2 NEONATAL

Neonatal morbidity and mortality including:

1. Neonatal death or stillbirth
2. Bronchopulmonary dysplasia,
3. Pulmonary interstitial emphysema
4. Retinopathy of prematurity
5. Pulmonary hypoplasia
6. Necrotizing enterocolitis
7. Patent ductus arteriosis
8. Seizures
9. Intraventricular hemorrhage
10. Periventricular leukomalacia
11. Sepsis

4.15.2.3 INFANT

1. Radiographic appearance of the Chiari II malformation - measured in millimeters of cerebellar herniation below the foramen magnum. Copies of the head MRIs will be forwarded to the DSCC for central reading by the Radiology Review Committee. Since there is no uniform grading scale available, the Radiology Review Committee in consultation with the pediatric neuroradiologists from the MOMS Centers will develop a grading system for the Chiari malformation based on:

   - Location of cerebellar tonsils in relation to the foramen magnum
   - Presence and location of a cervicomedullary kink
   - Size and location of the fourth ventricle
   - Additional secondary criteria, including the presence of hydrocephalus

   Review of the MRIs will be conducted by the Radiology Review Committee, blinded to the assigned surgery group of the infant.

2. Number of shunt revisions
3. Number of surgical procedures for related conditions such as tethered cord, hydrosyringomyelia, feeding problems, gastrointestinal reflux, urinary or fecal control, genitourinary reflux, and orthopedic deformities including kyphoscoliosis by 30 months
4. Locomotion - independent ambulation vs. braces vs. wheelchair bound at 30 months'

5. Brain stem function as measured by swallowing profile and BSAER tests
6. Motor scales from the Bayley Scales of Infant Development
7. Rating of functional impairment from the Gross Motor Function Classification System
8. Number of days of total hospitalization for the infant (through 30 months)

5 STATISTICAL CONSIDERATIONS

5.1 SAMPLE SIZE AND POWER

Although there are two primary outcomes, an adjustment for two comparisons to type I error was not included in the calculation of sample size. The outcomes may well be correlated and they may be of differing clinical significance.

5.1.1 DEATH OR VP SHUNT

Among 416 children followed at the Spina Bifida Clinic at CHOP, the overall shunt rate at one year of age was 84%. However, it is very possible that the shunt rate observed in the trial for the postnatal surgery group will be lower; therefore a range of shunt rates are considered. A 30% reduction in shunt rate (among survivors) would be considered clinically significant. Although higher apparent reductions from historical shunt rates have been shown among the surgeries performed before 25 weeks at both CHOP and Vanderbilt, it is possible that a smaller reduction will be observed in the trial, since many potential confounding factors and biases will be removed.

Table 6 below shows total sample sizes required for power 80%, type I error 5% 2-sided, using the method of Casagrande, Pike and Smith.[38] The primary outcome rates were calculated assuming 0, 5% and 10% death rate in both groups, a shunt rate in survivors of 70-80% in the postnatal group and at least a 30% reduction in the prenatal surgery group. The sample size was adjusted for a loss to follow-up rate of 5%.

TABLE 6: SAMPLE SIZES FOR VARIOUS SHUNT RATES AND DEATH RATES BY 1 YEAR OF AGE; POWER 80%, TYPE I ERROR 5% 2-SIDED, WITH 5% LOSS TO FOLLOW UP

1-year death rate in postnatal and prenatal surgery groups	1-year shunt rate in survivors - postnatal surgery group	1-year shunt rate in survivors - prenatal surgery group (30% reduction)	Primary outcome rate in postnatal surgery group	Primary outcome rate in prenatal surgery group	Reduction in primary outcome	Total sample size	Sample size adjusted for loss to follow-up
0%	70%	49.0%	70.0%	49.0%	30.0%	188	198
	75%	52.5%	75.0%	52.5%	30.0%	158	168
	80%	56.0%	80.0%	56.0%	30.0%	132	140
5%	70%	49.0%	71.5%	51.6%	27.9%	204	216
	75%	52.5%	76.3%	54.9%	28.0%	171	180
	80%	56.0%	81.0%	58.2%	28.1%	142	150
10%	70%	49.0%	73.0%	54.1%	25.9%	222	248
	75%	52.5%	77.5%	57.3%	26.1%	185	206
	80%	56.0%	82.0%	60.4%	26.3%	154	172

Given a death rate in both groups of 5% (fetal and neonatal deaths), the actual reduction in the composite outcome would be about 28%. In the fetal surgery cases to April 2002, the one-year death rate is 5.2% (11/212). Overall, assuming a primary outcome rate in the postnatal surgery group of 80%, a total of 100 patients per group will yield over 90% power to detect a 28% reduction, with 5% loss to follow-up.

5.1.2 COMPOSITE OUTCOME OF BAYLEY SCALES OF INFANT DEVELOPMENT MDI SCORE AND MOTOR FUNCTION

The second primary outcome is a composite of:

a) Bayley Scales of Infant Development mental developmental index MDI, and

b) Motor function, calculated as the difference between anatomic and functional level.

The anatomic and function level will be measured as described in Luthy, et al.[35] Functional and anatomic lesion level are scored from 1 (C1) to 29 (S5) with 30 indicating no motor impairment. Due to the inclusion criteria, anatomic lesion level can range from T1 (scored as 9) to S1 (scored as 26). Motor function will be scored as functional level - anatomic level. The highest score possible mathematically would be in a child with an anatomic lesion level of T1 and no motor impairment, or 30-9 = 21. Negative scores are possible for the child with lower functional level than predicted by lesion level. The lowest negative score possible mathematically would be in a child with an anatomic lesion level of S1 and a functional level of T1, or 9-26 = -17. Death can be assigned a score of -18. For the Bayley MDI, death can be represented by zero.

As proposed by O'Brien[39] a composite measure of both factors (the Bayley MDI and functional minus anatomic level) will be created by ranking the measurements for each factor separately and calculating the sum of the ranks for each individual. For example, if an infant has the highest Bayley MDI and the most improvement in functional level compared with the anatomic level, his or her rank sum will be 200. The advantage of using a method based on ranks is that death is taken into account by assigning the lowest rank: an infant that dies will receive a rank sum of 2. Under the null hypothesis that there is no difference between the two groups and if the two measures are independent (i.e., the Bayley Mental Developmental Index is independent of the improvement in expected motor function level) the mean and variance of the rank sum is a constant depending only on sample size. Under the alternative hypothesis that there is a difference between the prenatal and postnatal surgery groups, however, the mean and variance of the rank sum depends on the probability that an observation drawn at random from one group (say, fetal surgery) is larger than an observation drawn from the other group (postnatal surgery) as well as similar joint probabilities based on the relationship between several observations. Death can be taken into account when calculating these probabilities. For example, if X is an observation from the prenatal surgery group and Y an observation from the postnatal surgery group then the probability that X is greater than Y, P(X > Y), is given as follows:

$$P(X > Y) = P(X \text{ is a survivor}) \cdot P(Y \text{ is a death}) + P(X > Y \text{ given X and Y both survivors}) \cdot P(X \text{ is a survivor}) \cdot P(Y \text{ is a survivor})$$

since if X represents a death it is assigned the lowest possible score and cannot be greater than Y. If death rate d is observed in both groups, this becomes

$$P(X > Y) = (1 - d)\, d + (1 - d)^2 P(X > Y \text{ given X and Y are both survivors}).$$

Although the rank sum does not have a normal distribution and the rank sums for individuals are correlated, the central limit theorem can be invoked[39] and the normal distribution used to calculate power and sample size. O'Brien showed that a test based on this rank sum performs reasonably well.

There is more than 90% power to show a difference in rank sum, or effect size, of 0.5 standard deviations. However, this does not have intuitive meaning and it is useful to relate this to the differences which might be observed in the Bayley MDI and the functional minus anatomic level. Under the assumption that for survivors the Bayley MDI and the functional minus anatomic level have a bivariate normal distribution and that the two groups have equal variances, it is possible given various death rates and correlations between the two measures among survivors to calculate the power to show a difference between the two treatment groups given a sample size of 95 in each group, to account for 5% loss to follow up.

From data on 34 infants born following fetal surgery at CHOP, the mean and standard deviation of the difference between the anatomic and functional levels was 1.65 and 2.3 segments, respectively. Therefore 2.5 segments is a reasonable estimate of the standard deviation and is also consistent with Luthy et al.[32] The table below shows the power for mean differences of 1 segment or 0.4 standard deviations and 1.25 segments or 0.5 standard deviations. The Bayley MDI is assumed to have a standard deviation of 15. Thus a mean difference of 5 points is equivalent to one third of a standard deviation, and 10 points to two thirds.

As can be seen in the table below, both the correlation between the two measures and increasing the death rate tend to reduce the power.

TABLE 7. POWER FOR VARIOUS DIFFERENCES IN BAYLEY MEAN MDI AND FUNCTIONAL MINUS ANATOMIC LEVEL (ASSUMING A NORMAL DISTRIBUTION) AND THE CORRESPONDING STANDARDIZED DIFFERENCE IN MEAN RANK SUM

1-year death rate in postnatal and prenatal surgery groups	Correlation between Bayley MDI and functional - anatomic level among survivors	Difference in mean Bayley MDI	Difference in mean functional - anatomic level		
			No difference	1 segment 0.4 sd	1.25 segments 0.5 sd
0%	0	No difference		47.5%	65.8%
		5 points: 0.33sd	35.3%	93.9%	97.9%
		10 points: 0.67sd	88.1%	99.9%	99.9%
	0.25	No difference		40.0%	56.6%
		5 points: 0.33 sd	29.6%	88.4%	94.8%
		10 points: 0.67sd	80.6%	99.6%	99.9%
	0.5	No difference		34.5%	49.4%
		5 points: 0.33sd	25.5%	82.2%	90.6%
		10 points: 0.67sd	73.3%	98.7%	99.6%
5%	0	No difference		34.8%	49.5%
		5 points: 0.33sd	25.8%	81.7%	90.0%
		10 points: 0.67sd	72.7%	98.4%	99.4%
	0.25	No difference		30.5%	43.7%
		5 points: 0.33sd	22.7%	75.6%	85.2%
		10 points: 0.67sd	66.0%	96.8%	98.7%
	0.5	No difference		27.2%	39.0%
		5 points: 0.33sd	20.3%	69.8%	80.2%
		10 points: 0.67sd	60.2%	94.7%	97.4%

TABLE 7. POWER FOR VARIOUS DIFFERENCES IN BAYLEY MEAN MDI AND FUNCTIONAL MINUS ANATOMIC LEVEL (ASSUMING A NORMAL DISTRIBUTION) AND THE CORRESPONDING STANDARDIZED DIFFERENCE IN MEAN RANK SUM (CONTINUED)

1-year death rate in postnatal and prenatal surgery groups	Correlation between Bayley MDI and functional - anatomic level among survivors	Difference in mean Bayley MDI	Difference in mean functional - anatomic level		
			No difference	1 segment 0.4 sd	1.25 segments 0.5 sd
10%	0	No difference		25.7%	36.7%
		5 points: 0.33sd	19.3%	66.2%	76.6%
		10 points: 0.67sd	56.5%	92.4%	95.9%
	0.25	No difference		23.3%	33.3%
		5 points: 0.33sd	18.2%	61.2%	71.8%
		10 points: 0.67sd	55.2%	89.4%	93.9%
	0.5	No difference		21.4%	30.4%
		5 points: 0.33sd	16.3%	56.8%	67.4%
		10 points: 0.67sd	47.8%	86.3%	91.5%

For example, if the Bayley MDI and the difference in functional and anatomic levels have a correlation as high as 0.25, the death rate is 5% and in the fetal surgery group there is a 5 point increase in mean MDI and 1 segment improvement in mean difference between the anatomic and functional level, there would be 85% power to show a difference. If the Bayley score and the motor function score were independent, then there would be over 90% power to show a difference. The latter combination would be equivalent to an overall effect size of 0.5 standard deviations.

5.1.3 SECONDARY OUTCOMES

A sample size of 200 patients will also yield reasonable power for the secondary outcomes. For the rating scale of Chiari malformation, which is an ordered categorical outcome, power may be calculated based on the proportional odds model.[40] If in the postnatal surgery group, 5%, 50%, 30% and 15% had Chiari grades 0-1, 2, 3 and 4+ respectively (see Table 4), there would be between 70% to 80% power to detect an odds ratio of 2.0 (as was observed) for fetal surgery to yield a given grade or better versus worse than that grade.

5.2 ANALYSIS PLAN

5.2.1 INTERIM ANALYSIS OF OUTCOMES

During the trial, the external Data and Safety Monitoring Committee will meet periodically to review trial results. Interim reports analyzing the primary outcome pose well-recognized statistical problems related to the multiplicity of statistical tests conducted on the accumulating data. The timing of the interim analyses is at the discretion of the Data and Safety Monitoring Committee. The group sequential method of Lan and DeMets will be used to characterize the rate at which the type I error is spent. The chosen spending function is the Lan-DeMets[41] generalization of the O'Brien-Fleming boundary. This method is flexible with regard to the timing of the interim analyses.

The Data and Safety Monitoring Committee may also be consulted at any time if safety concerns arise during the conduct of the study. In this trial the primary outcome

determinations are remote from delivery yet the perinatal period is probably the time of greatest risk of death for fetuses undergoing the experimental treatment. The DSCC will continuously monitor cases of fetal/neonatal mortality during the trial, i.e., whenever an adverse event notice of death is received. If Fisher's exact test were to show evidence of harm with a nominal p-value < 0.1, the coordinating center would contact the NICHD representative on the DSMC and the Chair of the DSMC who would then decide whether to suspend recruitment and/or call a meeting or conference call to review the data. Alternatively, the DSMC may consider it desirable to set up a stopping boundary for this outcome as suggested by Bolland and Whitehead.[42] The fact that fetal or neonatal death would be included as a component of the primary outcome complicates the statistical interpretation, but as the authors note, "the ethical requirement to monitor safety is of far greater importance than the preservation of the mathematical purity of the efficacy analyses." However, p-values for efficacy calculated ignoring the safety rule would, if anything, be conservative.

Even though recruitment will end before virtually any primary outcome data is available, a formal interim analysis will take place before the final follow-up data are accrued but after seven months of follow-up to determine if the boundary has been crossed. Conditional power analyses will be calculated under various hypotheses. The DSMC may then be able to make a recommendation to the MOMS Centers regarding offering fetal surgery to patients outside of the trial.

Before each DSMC meeting, a formal detailed statistical report will be written based on all existing study data as of four to six weeks before the meeting (recruitment updates and other updated information can be brought to the meeting, as required). The report presents the results of every aspect of the study,[43] including baseline variables, protocol adherence, outcome variables, adverse events reported and MOMS Center performance in terms of recruitment, data quality, loss to follow-up and protocol violations. For the evaluation of the primary outcome, a different cohort of patients is chosen consisting of all patients randomized before a certain date so that selection bias does not directly or indirectly affect the study results.

5.2.2 PRIMARY ANALYSIS PLAN

All statistical analyses will be based upon the total cohort of patients randomized into the trial. Although data on some patients may be missing at points in time, all relevant data available from each patient will be employed in all analyses. Patients will be included in the surgery group to which they are randomly assigned regardless of compliance. It is generally agreed that analysis according to this "Intention to Treat" principle provides the most unbiased assessment of the true therapeutic benefits of a treatment.[37,44,45]

The primary analysis of the shunt/death outcome will consist of a simple comparison of binomial proportions. The relative risk and confidence interval will be reported. The individual components of this composite outcome will also be examined in addition to an analysis of the actual placement of the shunt as opposed to the need for a shunt. Although as stated above, the intent to treat principle should be applied, in the presence of losses to follow-up this is not possible unless an assumption is made regarding the outcome of those lost. Thus, the primary comparison will not include the lost to follow-up patients. However, a sensitivity analysis will be performed including these patients, with different assumptions

regarding their outcome, to determine whether the results are robust. A sensitivity analysis will also be performed to examine whether actual placement of the shunt versus meeting criteria for a shunt affects the study conclusions. Stratified analyses will be conducted, in particular by lesion level, gestational age and center, all of which have been shown in previous analyses to be related to the outcome. Interactions will be evaluated.

A similar strategy will be employed for the Bayley MDI/Motor Function composite score. Although the power analysis is based on a parametric analysis, the Mann-Whitney (Wilcoxon) test will be used to compare the two groups. The Wei-Lachin[46] method will be used to conduct stratified analyses, adjusting for environmental factors such as parent education level and socioeconomic status.

5.2.3 SECONDARY ANALYSIS

Many of the baseline and outcome measurements are qualitative. For example, biodemographics, complications of the antenatal, intrapartum, postpartum and neonatal period are predominantly dichotomous responses (i.e., yes, no). For these measurements, standard statistical methods for rates and proportions are appropriate.[47] For baseline and outcome measures that are quantitative (e.g., anthropometrics, blood pressure) and, standard parametric and nonparametric statistical methods, such as the Wilcoxon Rank Sum test, are appropriate. Time elapsed to the occurrence of an event is another type of variable encountered, such as latency of the pregnancy or time to shunt failure. For such measurements, life-table analyses are used to compare differences between groups[48] and the logrank test or related statistics[49] can be employed to test differences between survival curves. An extension of survival analysis or time to a single event is the possibility for multiple recurrent events over time in each patient, such as surgeries for shunts or preterm labor episodes. A family of statistical methods based on the theory of counting processes can be applied to such data.[50] For variables that are ordinal such as rating of functional impairment and functional level from the Manual Muscle test, the Mantel-Haenszel test of trend will be used.

For some outcomes, response of each study participant may be observed on two or more occasions. Standard linear models for repeated measures data will be applied to these data.[51] For Gaussian random variables, these include the linear model with structured covariance matrices[52] and the random-effects model.[53] For non-parametric analysis, the methods of Wei and Lachin,[46] may be used. Binary repeated measures, for example the presence or absence of a certain symptom, may be analyzed using the generalized estimating equation (GEE) model.[54,55]

In the analysis of clinical trials it has been traditional first to perform an overall assessment of treatment effect on the total cohort of patients, and then to perform various other analyses aimed at obtaining an adjusted assessment of treatment effectiveness, for example, adjusting for stratification factors used in randomization (clinical center) or other baseline patient characteristics (covariates). The objectives of these analyses include estimating the influence of covariates on the outcome and using covariates to improve the estimated difference of treatment groups.[56] The simplest such adjustment is a stratified adjustment, such as the Mantel-Haenszel procedure. A regression model, such as linear, logistic, or proportional hazards, depending on the type of outcome variable and on the fit, may be used to provide an interpretable adjustment for multiple baseline covariates simultaneously. The

proportional odds logistic regression model may be used for ordinal measures such as the grading scale for the Chiari malformation or the Gross Motor Function scale.

A stepwise procedure for model building can be employed to select a subset of covariates that appear optimal but, because there is considerable ambiguity as to the statistical confidence one can have in the results of such selection procedures, split-half, jackknife or other model validation methods would also be applied.[57] These analyses are considered exploratory in nature and are not viewed as providing confirmatory tests of hypotheses or as describing causal associations. Rather, findings observed in such analyses are viewed with caution and used as a basis for consideration of future studies designed to test specific hypotheses.

Models that employ baseline covariates can be directly interpreted because of the temporal relationship between the observation of the baseline covariate, the initiation of the randomly assigned treatment, and the observation of the outcome. An important class of analysis concerns confounding factors arising post randomization, or time dependent covariates. If the covariate may be considered as an inherent patient characteristic, independent of surgery group allocation, then it can be included as a time dependent covariate in the models above, but it is quite plausible that for example, a factor measured at delivery, is correlated with the surgery group allocation, and including both in a linear model may result in invalid results. Analysis involving time dependent covariates must be carefully interpreted.

5.2.4 RACIAL/ETHNIC SUBGROUP ANALYSIS

Power is limited to detect moderate differences in the primary outcomes within the racial/ethnic subgroups; however, this analysis is planned and if, for example shunt outcome is as dramatic as preliminary data suggest, there will be sufficient power (86%) with type I error 5% 2-sided, using Fisher's Exact test to detect a difference from 80% to 30% among Hispanics, if there are as many as 40 Hispanic patients. This kind of difference was seen at CHOP when compared with historical controls. Even for the other minorities, of whom about 27 patients are expected, there is 68% power.

6 DATA COLLECTION

6.1 DATA COLLECTION FORMS

Data will be collected on standardized forms on which nearly all responses have been precoded. Forms will be mailed in on a weekly basis. The Randomization Form will, however, use a web-based data entry system since it will be linked to the Internet randomization procedure. The data collection forms are described briefly below. The first two forms are completed at the DSCC before referral to the MOMS center; the remaining forms are completed at the MOMS centers.

- SCR0: Initial Contact Form (completed for all interested parties at initial contact with the DSCC)
- SCR1: Central Screening Log (completed by the DSCC staff during central screening process)
- SCR2: Central Screening Form (completed by the DSCC after screening consent obtained and medical records reviewed)
- MOM1: Patient Evaluation Form (screening information completed for a patient referred to the MOMS center; result of randomization assignment and reason for non-randomization, if applicable).
- MOM2: Psychosocial Evaluation Form (provides data on psychosocial evaluation and psychological testing prior to randomization)
- MOM3: Baseline Data Form (includes baseline demographics, medical history and current pregnancy history)
- MOM4: Previous Pregnancy Log (lists previous pregnancies and the general outcome of each)
- MOM5: Maternal/Fetal Surgery Form (for patients assigned to fetal surgery group, details of the surgery and hospital course)
- MOM6: Monthly Prenatal Visit Form (documents ultrasound parameters, tocolysis etc.)
- MOM7: Maternal Hospital Admission form (hospital admissions for complications)
- MOM8: Labor and Delivery Form (documents delivery information, including intrapartum or postpartum complications through discharge)
- MOM9: Neonatal Baseline Form (records anthropometric measures, Apgar scores and specific neonatal complications detectable at birth)
- MOM10: Neonatal Outcome Form (records specific neonatal complications and problems requiring admission to the NICU)
- MOM11: Postnatal Surgery Form (for infants repaired postnatally)
- MOM12: Infant Hospital Admission Form (documents rehospitalizations and emergency outpatient visits since discharge following birth)
- MOM13: Protocol Deviation/Withdrawal Form
- MOM14: Adverse Event Form
- MOM15: CNS MRI/Ultrasound/X-ray Log (documents imaging studies performed for the trial and sent for review)
- MOM16: Shunt Placement Form (documents specific indications for shunt placement and the consultation process)
- MOM17: Quarterly Infant and Parental Follow-up Form
- MOM18: Twelve Month Examination Form

- MOM19: Thirty Month Examination Form

Additional forms will be developed in-house for recording the results of the Shunt Outcome Review Committee and the Radiology Review Committee.

6.2 CENTRAL DATA ENTRY SYSTEM

Data will be keyed at the DSCC into PC based data entry software set up to require validation of out of range values. Corrections or 'updates' received in writing at the DSCC in response to edit or audit messages (see below), are keyed together with incoming data forms. The core system is written in Visual FoxPro 6.0, with object-oriented design. Case report forms are keyed once and then independently re-keyed by the data entry operator.

6.3 CENTRALIZED DATA MANAGEMENT SYSTEM

Once the data are keyed, they will be uploaded to the server on a weekly basis The data processing entails both the addition of new data to the study database on the central server and the editing of new or replaced records. The newly entered records are added to permanently stored SAS data sets containing all data for the study. These will constitute the permanent study database. Records replaced in the updating procedure are added to a secondary file to form an 'edit trail' within which changes to the data over time may be traced.

The new and updated data are automatically edited using software developed in SAS on an intra-form basis. Intra-form edits include checks for items that should have been answered but are missing, items that should have been skipped but were completed instead, values that are out of range, and any other logical inconsistencies between items on a form. After review at the DSCC, edit printouts are returned to the center for correction or clarification on a weekly basis. At regular intervals, audit programs (also in SAS), which compare data across forms are run by the DSCC on the entire database or on a specific subset of data. Inter-form audits include checks for inconsistencies in a study participant's clinical profile, in date sequences, or on unlikely values for repeated measurements. These include longitudinal checks that compare forms over time (e.g., forms completed at an earlier visit with forms completed at a subsequent one). Audit reports are also submitted to the centers for correction.

Any problems detected by the software are logged into a permanent database which records the forms, fields, and values that were involved, the nature of the problem as well as information that allows the software to track the edit or audit until it is resolved.

6.4 PERFORMANCE MONITORING

The Steering Committee will assume overall responsibility for the management and conduct of the trial. This includes monitoring the performance of their own centers in terms of data quality, protocol adherence and recruitment.

The DSCC will make the following tools available to the Steering Committee for performance monitoring.

- Data Quality Reports: The DSCC will report to the Steering Committee on the volume of edits and audits (presented as the number per 1000 fields keyed), the time to edit resolution and the number of overdue forms. Data quality tables will be presented by center and time period, to identify both center and temporal problems. Data quality reports will be included in the Steering Committee reports that are generated quarterly.

- Performance Reports: The DSCC will generate reports of study progress on a monthly basis (recruitment reports) and on a quarterly basis (Steering Committee reports). The recruitment report will include enrollment efforts (screening numbers, reasons for ineligibility, recruitment numbers) by MOMS Center and will be distributed by e-mail. Full Steering Committee reports will be prepared quarterly to coincide with the meetings and conference calls. These reports will be more extensive than recruitment reports and will include recruitment data, protocol adherence data such as study participants apparently lost to follow-up or overdue, protocol violations, baseline characteristics, and data quality assessment.

In addition, the DSCC will report on center performance to the Data and Safety Monitoring Committee. For every meeting of the DSMC, a report is prepared which includes patient recruitment, baseline patient characteristics, center performance information with respect to data quality, timeliness of data submission and protocol adherence, in addition to analysis of outcomes.

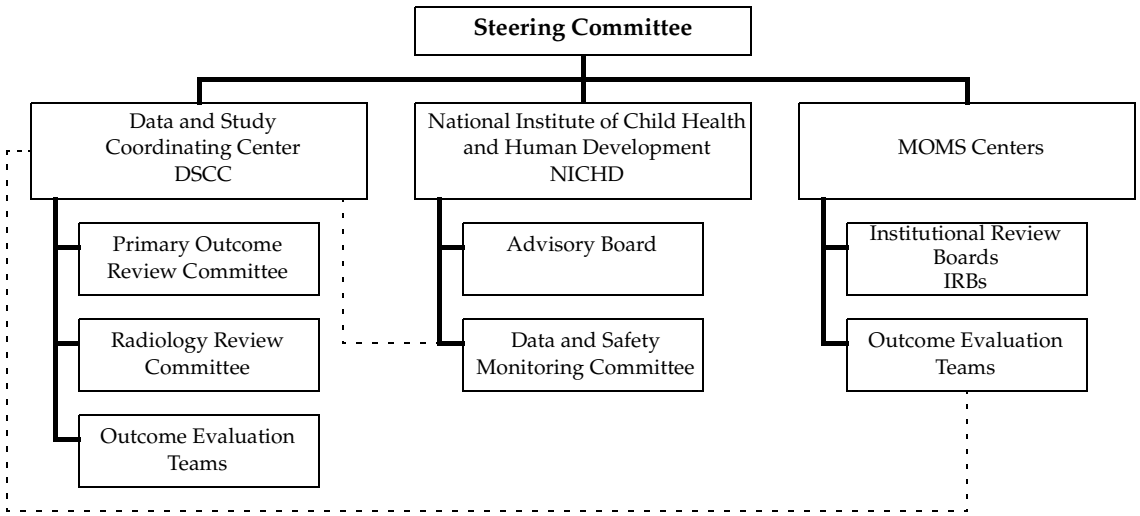
7 STUDY ADMINISTRATION

7.1 ORGANIZATION AND FUNDING

The study is being funded by the National Institute of Child Health and Human Development (NICHD). The study will be conducted by three MOMS Centers, the Data and Study Coordinating Center and NICHD, and is administered under cooperative agreements between each of the centers and NICHD. The study will be conducted under the auspices of the NICHD MFMU Network, although the three MOMS Centers do not coincide with any of the MFMU Network clinical centers. However, the data coordinating center of the Network will function as the DSCC for the Fetal Surgery Units Group; the MFMU Network Advisory Board and the Data and Safety Monitoring Committee will also serve the group.

A Principal Investigator represents each of the funded institutions. A diagram of the study organization is presented and each component described below.

FIGURE 2. STUDY ORGANIZATION



7.1.1 PARTICIPATING CLINICAL CENTERS

The Principal Investigators of the three MOMS Centers have agreed to abide by the study protocol, to have comparable staff, facilities and equipment and to ensure the proper conduct of the study at each of their centers including: recruitment and treatment of patients as specified in the protocol, accurate data collection and the transmission of information to the Steering Committee.

7.1.2 DATA AND STUDY COORDINATING CENTER

The Data and Study Coordinating Center (DSCC) is responsible for all aspects of biostatistical design, analysis and data management of the study, in addition to the interim and final statistical analyses and preparation of publications based on the study results. For this trial, the DSCC will also be responsible for advertising the trial, serving as a referral center for interested patients or the public, and for coordinating the outcome evaluations,

including both the review of MRIs and ultrasounds, as well as the infant follow-up examinations. The Principal Investigator of the DSCC reports to the Steering Committee and the Data and Safety Monitoring Committee.

7.1.3 NICHD

In addition to its role as funding agency, the NICHD participates in the activities of the Network, including the development of the protocol, administration and conduct of the study and preparation of publications.

7.1.4 MFMU NETWORK ADVISORY BOARD

Appointed by the NICHD, the members of the MFMU Network Advisory Board consist of a group of experts representing the disciplines of maternal-fetal medicine, neonatology, biostatistics and epidemiology who are not affiliated with research being conducted by the Network. Additional ad-hoc members with expertise in neonatal/fetal surgery and perinatal ethics will be added for this trial. The role of the board includes reviewing the proposed study, in addition to identification of scientifically and clinically important questions that the study could feasibly be modified to answer. The NICHD program officer convenes and attends the meetings.

7.2 COMMITTEES

7.2.1 STEERING COMMITTEE

The Steering Committee will be the policy and decision-making group, and assume overall responsibility for the management and conduct of the trial. This committee consists of five members. The Principal Investigator from each of the three MOMS Centers and the Data and Study Coordinating Center, and the NICHD MFMU Network Program Scientist are all voting members. Dr. Mary D'Alton, who is not affiliated with any participating center chairs the Steering Committee. The Chairman of the Steering Committee may vote to break a tie. Steering Committee meetings will be held twice per year during recruitment, once per year thereafter, with interim videoconference calls quarterly. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

Unlike the MFMU Network, there will be no separate Publications Committee. However, the Publications Policy developed by this committee will be used as basis for a publications policy for this study group (see publication policy, below).

7.2.2 DATA AND SAFETY MONITORING COMMITTEE

The DSMC is a group of individuals not affiliated with any of the participating MOMS Centers and free of real or apparent conflict of interest. This committee is established by the NICHD for the MFMU Network and represents expertise in ethics, clinical trial design, perinatology, neonatology and basic science. Ad-hoc members with expertise in pediatric/ fetal surgery and perinatal ethics will be included for this trial. The DSMC is charged with reviewing the protocol with respect to ethical and safety standards and making recommendations as necessary. This committee will monitor the emerging results for safety

and efficacy. The DSMC will also review the performance of the trial in terms of recruitment, protocol adherence and data quality. The interval and timing of DSMC meetings after the initial review of the protocol is at the discretion of the committee itself.

7.2.3 LOCAL OVERSIGHT COMMITTEES

Each MOMS Center will form a multidisciplinary local Oversight Committee, including local expertise in the areas of adult/obstetric intensive care, obstetrics/maternal fetal medicine, neonatology, neurology/neurosurgery, nursing, pediatric surgery, and social work. Membership of the committees will include IRB appointees and they will meet on a monthly basis to review local fetal surgery cases, and progress of previous cases. The DSCC will create a monthly report for each committee consisting of patient information at a case-by-case level, in addition to any adverse event reports received. Each committee would make recommendations to the local PI and Institutional Review Board (IRB) and would be housed in the Chief of Staff Office (Quality Assurance). Both this committee and the IRB will receive reports of all DSMC meetings.

7.2.4 SHUNT OUTCOME REVIEW COMMITTEE

The Shunt Outcome Review Committee will review clinical notes, case report forms and imaging studies of all infants to determine if they did or did not meet the criteria outlined in the protocol for shunt placement. The committee will be comprised of three independent pediatric neurosurgeons. One of the members of the Radiology Review Committee will also take part.

7.2.5 RADIOLOGY REVIEW COMMITTEE:

The Radiology Review Committee will review the MRIs obtained at enrollment, discharge or term, and one year of age to determine the grade of the Chiari II malformation and the presence of a tethered cord. The committee will be comprised of two independent pediatric neuroradiologists with the addition of a pediatric radiologist who specializes in prenatal diagnosis.

7.2.6 OUTCOME EVALUATION TEAMS:

Three or more Outcome Evaluation Teams will be set up, each comprised of an independent developmentalist and psychologist/psychometrist, and DSCC staff. These teams will conduct the infant neurologic and developmental examinations in a standardized manner and ensure the follow-up data are collected completely and accurately.

8 STUDY TIMETABLE

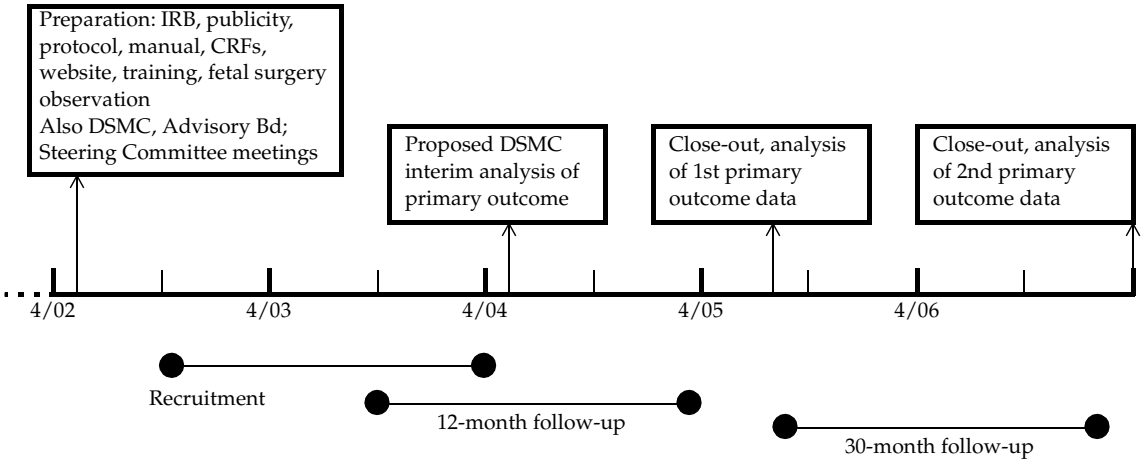
8.1 TRAINING AND CERTIFICATION

Prior to the start of the trial, training of research personnel on the contents of the manual of operations will take place. Each center will be required to fulfill certification requirements, including a demonstration of familiarity with the protocol procedures, eligibility criteria and definitions for the case report form fields.

8.2 RECRUITMENT AND DATA COLLECTION PERIOD

The timeline for the trial is summarized in the figure below.

FIGURE 3. TIMELINE



Funding began in April 2002 and the first Steering Committee meeting was held in May 2002. Randomization is scheduled to begin in October 2002.

A Steering Committee meeting is proposed shortly after the start of recruitment to evaluate study progress and implement solutions to any problems During this year final preparations will be made for the neurologic and neurodevelopmental follow-up, including development of the case report forms and the manual of operations and training of the Outcome Evaluation teams.

Overall, it is anticipated that randomization of 200 patients will take 18 months to April 2004. From the CDC data of 1999, by which year the effects of folic acid supplementation had become apparent, it is estimated that during an interval of this length there would be about 1100 births with spina bifida across the United States. If this represents the number of women diagnosed with myelomeningocele and committed to maintaining their pregnancy, then less than 20% will be needed to complete randomization in 18 months.

It is proposed that a formal interim analysis of the first primary outcome be conducted in May 2004, after seven months of follow-up, to be presented to the DSMC. Closeout and analysis of the first primary outcome will take place in July 2005.

The thirty month exams should be completed by January 2007.

8.3 FINAL ANALYSIS

Closeout and analysis of the primary outcome results will be initiated in January 2007. The last three months of the project will be used for closeout and final analysis and manuscript preparation of the follow-up results.

8.4 PUBLICATION POLICY

Publication of individual results by the participating centers is unacceptable. All publications will be under the auspices of the "Fetal Surgery Network".

Press releases, announcements, and other publicity will be handled by NICHD. All of the PIs and major co-investigators will be invited to any press conferences. The Program Scientist at NICHD will be the primary study representative at this press conference. At the conclusion of the initial press conference, the PIs will be free to respond to inquiries from local and regional media.

There will most likely be several manuscripts resulting from this study. The first author for each publication will be randomized among the four centers (the three MOMS Centers and the Biostatistics Center). The order of the remaining authors will randomized.

APPENDIX A. DESIGN SUMMARY

A Randomized Trial of Prenatal and Postnatal Myelomeningocele Repair

OBJECTIVE

To determine if intrauterine repair of fetal myelomeningocele (MMC) at 18^0 to 25^6 weeks gestation improves infant outcome as measured by 1) death or the need for ventricular decompressive (VP) shunt by 12 months and 2) death or a composite of the Bayley Scales of Infant Development (BSID) Mental Developmental Index (MDI) and the difference between the anatomic and the functional level of the lesion by 30 months corrected age as compared with standard postnatal repair

ORGANIZATION

Clinical Centers/ MOMS Centers (MOMS Centers):	• University of California-San Francisco; Vanderbilt University, Children's Hospital of Philadelphia
Data and Study Coordinating Center (DSCC)	• George Washington University Biostatistics Center
Steering Committee:	• Dr. Mary D'Alton (chair), Dr. Michael Harrison, Dr. Joseph Bruner, Dr. Scott Adzick, Dr. Elizabeth Thom, Dr. Catherine Spong

DESIGN

Type:	Randomized clinical trial
Major Eligibility Criteria:	• MMC at T1-S1 w/ hindbrain herniation by MRI • 9^0-25^6 weeks gestation • Singleton pregnancy • Normal karyotype • Maternal age at least 18 years • Informed consent
Groups:	• Experimental: Prenatal repair of the MMC • Standard care: Postnatal repair of the MMC
Random Allocation:	Standard urn design
Level of Masking:	Unblinded
Stratification:	Clinical center
	Trial goal = 200 (100/group) Assumptions: 1) Type 1 error = 5% (2-sided); Power >= 90% 2) Outcome event = death or shunt at 12 mths • Standard care group event rate = 80% • Experimental event group rate = 28% reduction 3) Outcome score = BSID MDI rank + functional - anatomic level rank or death at 30 mths; where death=minimum score • Difference in mean outcome score = 0.5 standard deviations
Interim Analysis:	Group sequential method

SCHEDULED EVALUATIONS / DATA COLLECTION

Pre-randomization:	• History, level II U/S, amnio/CVS, MRI, counseling, psychosocial evaluation, physical exam
Post-randomization: (Maternal)	• Psychosocial evaluation at delivery, 12, 30 months; Reproductive functioning at 30 months
(Infant)	• Gestational age at delivery; neonatal morbidity • MRI at delivery, at discharge or 37 wks, 12 months • Neurologic exam, leg strength test and developmental testing at 12, 30 months corrected age • Brain stem evaluation (BSAER/ swallowing profile), urologic evaluation (urodynamics, renal sonography) at 30 mths, orthopedic, ophthalmologic evaluations

MANAGEMENT PROTOCOLS

Prenatal surgery group:	• Post operative care; discharge on tocolysis; bi-weekly ultrasounds and weekly prenatal visits • Stay nearby MOMS Center until delivery or return to assigned MOMS Center at 32 weeks gestation; lung maturity studies and cesarean delivery at 37 weeks
Postnatal surgery group:	• Standard prenatal care; monthly ultrasounds • Return to assigned MOMS Center at 37 weeks gestation for lung maturity studies and cesarean delivery • Repair of spina bifida when stable

OUTCOME MEASURES

Primary:	• Infant death or ventricular shunt by 1 year of life • Bayley Scales of Infant Development MDI and functional - anatomic level of lesion at 30 months corrected age
Secondary:	• Chiari II malformation • Neurodevelopmental status • Ambulation status, neuromuscular defects • Maternal psychological and reproductive functioning

TIMETABLE

Randomization	10/2002 - 04/2004
Data Collection	10/2002 - 01/2007
Closeout/final analysis	01/2007 - 04/2007

APPENDIX B. INFORMED CONSENT FORMS

B.1 CONSENT FORM FOR SCREENING

SCREENING INFORMED CONSENT FORM

Research Study	Myelomeningocele Repair Randomized Trial (MOMS)
Investigator	Elizabeth Thom, PhD.
Telephone Number	301-881-9260
Project Manager	Catherine Shaer, M.D.
Telephone Number	1-866-ASK-MOMS (866-275-6667)

I. INTRODUCTION

You have contacted us because you have heard about this research study and you might be interested in participating. We think you may be eligible, but before we can decide, we will need more information about you and your baby and we will need to review your medical records and may need to speak to your doctor. This process is called screening. This consent form provides information about the screening process for this research study. Dr. Catherine Shaer, the Project Manager, will be available to answer your questions and provide further information about the study. If you agree to be screened, you are asked to sign this consent form. Signing this form does not mean that you have made any decision, just that you will allow us to contact you and talk to your doctor and obtain and review your medical records. Later, if we find that you are eligible and you decide that you want to take part in the study, you will be asked to sign another consent form which will give you more details about the possible risks and benefits of participating in the study. This process is known as informed consent.

Your decision to let Dr. Shaer contact you with more information about the study and to allow Dr. Shaer to review your medical information and speak to your doctor if necessary is voluntary. Please do not hesitate to ask questions. You are free to choose whether or not you will be screened.

II. PURPOSE

The George Washington University Biostatistics Center is coordinating a research study to find out whether closure of spina bifida (myelomeningocele) while the baby is still in the mother's uterus (womb) is better for the baby's outcome than closure done soon after birth. The person in charge of coordinating this research study is Dr. Elizabeth Thom.

This research is funded by the National Institute of Child Health and Human Development (NICHD), a part of the National Institutes of Health (NIH).

III. PROCEDURES

Three clinical centers (Vanderbilt University Medical Center in Nashville, Tennessee, the University of California at San Francisco in San Francisco, California, and Children's Hospital of Philadelphia in Philadelphia, Pennsylvania) are doing this research study together with the George Washington University Biostatistics Center in Rockville, Maryland.

The study is being done to find out whether it is better to close a spina bifida defect before the baby is born or shortly after birth. Until recently, the only way to treat a baby with spina bifida was to do the surgery soon after birth. Now, at a very few places in the United States, there are specialized teams of doctors who are able to do surgery on a baby with spina bifida while the baby is still in the uterus (womb). They do this by opening her womb as though they were doing a C-section and closing the baby's spina bifida defect. The mother's womb is then sewn up, as for a C-section, and the mother and baby continue the rest of the pregnancy. The doctors think that they may be able to stop some damage to the baby's spinal cord and brain by doing the closure early in the pregnancy, but they don't know for sure. The purpose of this trial is to find out the answer to this question.

A total of 200 pregnant women over the age of 18 years, in the middle part of their pregnancy, will be enrolled. To qualify for the trial, their fetuses must have been diagnosed with spina bifida that is not too high up or to low down the back and the baby must have the Chiari II malformation, an abnormality of the brain which is commonly found in babies with spina bifida. Patients or their doctors will contact the Biostatistics Center for information. They will talk to Dr. Shaer, a trained pediatrician and expert in spina bifida, who will tell them about the study. Patients who consent to have their medical records reviewed by Dr. Shaer will be sent a package of information about the trial. Dr. Shaer will contact them to let them know if they seem to be eligible and to answer any questions they may have. If they are eligible and are still interested in participating, they will be assigned to one of the three clinical centers for further evaluation and for treatment if eligibility is confirmed. Women will not be able to select which clinical center they will be assigned to. They will be assigned to one of the three centers based on convenience to them as well as the need to evenly divide the participants between the three centers.

The patient will then contact their assigned center to arrange a date for further screening. She will travel to the center with the baby's father or another support person. Travel to the center and meals and lodging while they are there will be paid for. During this final screening process, they will get a lot of counseling to make sure that they understand the trial as well as to help them understand what the baby will need later in life. If the screening determines that they are still eligible and if they still want to take part in the study, they will be asked to sign an informed consent form. Then the staff at the clinical center will find out whether the patient will get either surgery before the baby is born (prenatal surgery), or surgery after the baby is born (postnatal surgery). There is a 50:50 chance being assigned to either group, like the chances of getting a heads or tails when flipping a coin. Because prenatal surgery is experimental, it will not be offered at the participating centers or other facilities in the United States outside the study once it begins.

Patients assigned to have prenatal surgery will have the surgery done soon after the assignment is made and they will stay at nearby accommodations until the baby is born by C-section. They need to stay near the MOMS Center to make sure that they get the best care and so that they may be watched for any signs of premature labor. They will be able to go home with the baby once the child is stable. This usually takes seven to ten days.

Patients assigned to postnatal surgery will return home until three weeks before their due date when they will come back to the center for delivery by C-section and subsequent closure of their baby's spina bifida defect by the MOMS team neurosurgeon. The spina bifida defect will be closed at the MOMS Center as soon as the baby is stable enough for surgery.

In both groups, the patients will travel back to the MOMS Center when the baby is one year old and two and a half year old for exams to find out how the baby is doing. By comparing the babies who had prenatal surgery with those who had postnatal surgery we may be able to find out whether prenatal surgery improves the babies' outcome.

IV. POSSIBLE RISKS

Detailed information about the possible risks of the study is outlined in the brochure that comes with this form. Dr. Shaer is available to discuss these risks with you in detail and to answer any questions you may have. If you get as far as going to one of the MOMS Centers for further screening, the risks will again be discussed with you in depth before you make a decision.

The main risk to the fetus or infant is the risk of being born too early (prematurely). This can result in lung problems, brain damage, or even death. So far, babies who have had this surgery before birth were born about 6 weeks early on average (34 weeks). About 1 in 10 were born more than 10 weeks early (earlier than 30 weeks). So far, seven babies have died due to premature birth out of 192 fetal surgeries. By staying close by the center to be monitored closely, and following the instructions of your healthcare team, the risk of delivering prematurely will be reduced as much as possible.

For mothers, the main risk comes from cutting the womb twice in the same pregnancy. This means that she will most probably have to have a C-section for all future deliveries. Rupture of the womb and the loss of amniotic fluid are also risks. The risks of wound infection and of complications from anesthesia are the same as they would be for any C-section. The mother will have to stay near the MOMS Center after surgery until she is ready to deliver, possibly for as long as 20 weeks. This could have a serious effect on all members of her family.

V. POSSIBLE BENEFITS

Again, the possible benefits will be discussed in more detail if you decide to find out more about this trial. If you are assigned to prenatal surgery, it may improve your baby's neurologic outcome. This means that your baby may have more function in the legs and more bowel and bladder control than if the surgery were not done. Babies in both the prenatal and postnatal surgery groups will get care from very experienced neurosurgeons at the three participating centers. The staff at the centers will also continue to monitor your baby's progress after you go home. They can also help you find doctors in your area who can take care of your baby's special needs. By taking part in the one-year and two and a half year exams, any problems that your baby has can be diagnosed and you will get help in finding care in your home area. Also, in the future, families facing this situation may benefit from information obtained from this study.

VI. ALTERNATIVES

One alternative to participating in this study is for your baby to have postnatal surgery. Prenatal surgery for spina bifida is not offered in the United States except in this study. Some women choose pregnancy termination. You have the right to refuse all treatment.

VII. COSTS

If you do choose to take part in the study, there will be no additional costs for prenatal care beyond those you would normally have. If you are in the prenatal surgery group, the travel, meal and lodging costs for you and a relative or friend will be covered until delivery and after delivery until you take the baby home. If you are in the postnatal surgery group, travel back to the center for you and a support person will be covered, as well as meals and lodging before and after delivery until your baby is able to go home with you. In addition, if you have insurance, the cost of all medical care associated with the study not covered by your insurance will be covered by the study. The cost of returning with your baby at one year and two and a half years of age will also be covered. Meals and lodging will be covered for those visits as well.

VIII. COMPENSATION

No financial compensation (no payment) is available for participants in this study.

IX. RIGHT TO WITHDRAW FROM THE STUDY

Your participation in this research study is voluntary. You may decide not to begin or to stop this study at any time.

X. CONFIDENTIALITY OF MEDICAL AND RESEARCH RECORDS

Your medical information will be kept as confidential as possible while you are deciding about the trial as well as later if you take part in the study. Your phone calls to and from the Biostatistics Center will be private because they will not go through the main switchboard. Dr. Shaer will have a separate FAX machine to get medical records from your doctors. Personal and medical information will be kept in a locked filing cabinet on a zip disk which will be locked away when Dr. Shaer is not in the office. If you decide you do not want to proceed with screening for this trial or if you are not eligible, all of your medical and personal information will be destroyed.

You have the right to privacy. All information obtained from this research that can be identified with you will remain as confidential as possible. Representatives of governmental agencies may review and photocopy your medical and research records to assure the quality of the information being used in the research.

If you do decide to take part in the trial, your medical data collected for this study will be sent to the George Washington University Biostatistics Center to be put into a database consisting of information from all of the participants in this study. The information in the database about you and your child will only be used for statistical analysis. The information or analysis may appear in scientific publications without identifying you. The medical data sent to the central database does not include your name, address, social security number, hospital number, date of birth or any other personal identifiers.

To help us protect your privacy, we have obtained a certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state or

local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

XI. QUESTIONS

For questions about study procedures, contact Dr. Shaer at 1-866-ASK-MOMS (866-275-6667). If you have questions about the informed consent process or any other rights as a research subject, please contact the Assistant Vice President for Health Research, Compliance and Technology Transfer at the George Washington University at 202-994-2995. This is your representative.

XII. SIGNATURES

By signing this consent form you affirm that you have read this informed consent form and you agree to be screened for this study. You do not give up any of your legal rights by signing this informed consent form. You will receive a copy of this consent form.

_____	_____	_____
Participant (Printed Name)	Signature	Date
_____	_____	_____
Authorized Representative	Signature	Date

Relationship to Participant _____

_____	_____	_____
Person Obtaining Consent	Signature	Date

A witness unrelated to the study is necessary if the participant can comprehend but cannot read (i.e. blind) or cannot sign (i.e. unable to use hands) the consent form.

_____	_____	_____
Witness's Name (Print Name)	Signature	Date

XIII. INVESTIGATOR'S STATEMENT

I certify that the screening process for this research study has been explained to the above individual by me or my research staff including the purpose, the procedures, the possible risks and the potential benefits associated with participation in the screening process for this research study. Any questions raised have been answered to the individual's satisfaction.

_____	_____	_____
Investigator's Name (Print Name)	Signature	Date

B.2 SAMPLE STUDY INFORMED CONSENT FORM

CONSENT TO PARTICIPATE IN THE MANAGEMENT OF MYELOMENINGOCELE STUDY (MOMS)

I. INTRODUCTION

You are being evaluated for voluntary participation in this research study. In order to fully understand what the study involves and what will be required of you, you need to understand the risks and benefits associated with participating. This process is known as informed consent. This form explains the study and what it requires. Please ask your study doctor or nurse to explain any words or points you do not understand.

II. BACKGROUND AND PURPOSE

Myelomeningocele, also called spina bifida, is a condition which occurs in the fetus when a part of the developing spinal cord and its coverings do not close properly. As a result, the undeveloped spine is open onto the back of the fetus. Babies with myelomeningocele are born with some degree of nerve damage which causes varying degrees of leg and foot weakness and paralysis, as well as poor or absent bowel and bladder control. In addition, they also have a problem with brain development called the Chiari II malformation. Individuals with the Chiari II most often have to have a tube (called a shunt) placed into the brain cavities (ventricles) after birth to relieve a build-up of fluid. This condition of fluid build-up in the brain cavities is called hydrocephalus.

You and your unborn child are being asked to participate in this research study because you are carrying a fetus with myelomeningocele that could possibly be treated by one of two methods: standard care which involves closure of the defect after birth (called postnatal repair) or closure before birth (called prenatal repair). At this time it is not known if either therapy is better, although surgery after birth has been the standard for many years. However, an operation has been developed which may benefit your unborn child. This operation is performed on a pregnant woman and her unborn child between the 19th and 25th week of pregnancy.

The goal of the prenatal operation is to protect the exposed spinal cord from further damage and prevent, reduce or reverse development of the Chiari II malformation. The doctors involved in this study have experimental and clinical evidence showing that, by closing the spinal cord before birth, development of the Chiari II malformation may be prevented or its severity reduced, and leg weakness may be improved. This treatment requires prenatal (fetal) surgery. The pregnant woman's abdomen and womb must be opened to close the exposed fetal spinal cord. Because this operation is new, we do not know if it is safe for pregnant women or unborn babies, or if it is effective in preventing or reducing the brain damage or nerve damage in an unborn child with spina bifida.

The other way to treat myelomeningocele is the standard method that does not involve surgery before birth. After a baby with spina bifida is born, standard postnatal care involves surgery to close the baby's exposed spinal cord. In addition, insertion of a shunt into the ventricles to relieve build-up of fluid within the brain is usually needed. Shunt placement is most often done during a second surgery.

The effectiveness of closing the spinal cord before birth in babies with myelomeningocele is not known. We do not know if the fetal surgical procedure is worth the risks involved, or if the results will be any better than those obtained with the standard postnatal surgery. Because of the many questions regarding these procedures, we are performing this study to determine whether prenatal surgery improves outcome compared to the standard of repair after birth.

In this study we will examine whether unborn children who have their exposed spinal cords closed using fetal surgery techniques do better, the same, or worse than unborn children treated for myelomeningocele after birth. If you chose to participate in the study, your baby will have either prenatal surgery or postnatal surgery performed by insert name of principal investigator and the MOMS Center team at insert name of institution.

III. PROCEDURES

A. ASSIGNMENT PROCEDURES

If you voluntarily agree to be enrolled in this research study, you will be assigned to a MOMS Center and you will travel there with your baby's father or another support person. You and the baby's father will be asked to take three brief psychological tests. You will then be randomly assigned to one of two groups, surgery before birth (prenatal surgery) or surgery after birth (postnatal surgery). This means that you and your unborn child have a 50% chance of being in either group, like the odds of getting a heads or a tails when flipping a coin. Neither you nor the doctors will make the choice of which group you and your unborn child are assigned to. Instead, the Data and Study Coordinating Center (DSCC) at the George Washington University Biostatistics Center will randomly assign you to surgery before birth or surgery after birth. Further surgery on your baby's spinal cord or surgery to place a shunt may be needed regardless of which group you are assigned to.

B. SURGICAL PROCEDURES

Surgery before birth group: If you are assigned to the prenatal closure group, you and your unborn baby will have surgery under general anesthesia when the fetus is between 19 and 25 weeks old. You will be admitted to the hospital on the day of surgery and asked to sign a separate consent form for surgery. An IV (a needle placed into a blood vessel under your skin to give fluids and/or medications) will be started in your arm. Prior to the operation, an epidural catheter will be placed in your back for use in controlling pain after the operation. You will be given general anesthesia, and that anesthesia will put your baby to sleep as well. In addition, your unborn baby will be given an injection of pain medication during the fetal surgery. After surgery, pain medication will be administered to you and will reach your unborn baby through the placenta.

a) Before the surgery begins you will be given one dose of indomethacin, a tocolytic drug, (see page 5) to prevent premature uterine contractions. The surgery involves making a horizontal incision (cut) in your abdomen. A vertical incision may be used if medically necessary or if you have a previous vertical scar. Ultrasound will be used to determine where it is safe to make the incision in your uterus. Magnification by special lenses or a microscope will be used to help the doctors perform the operation on your unborn baby's back. Antibiotics will be

put into the amniotic fluid remaining in your uterus and the opening in your uterus will be closed after the fetal surgery is completed.

b) You will be kept in the hospital until you are well enough to leave and your unborn baby is stable. This usually requires 3-7 days but may last as long as the pregnancy continues. For the first few days after surgery, you will be closely monitored. You will receive intravenous (IV) fluids and will have to stay in bed during most of this time. You will also be given magnesium sulfate (another tocolytic drug) for 48 hours to prevent premature labor which is a consequence and major complication of fetal surgery. You will also be given additional indomethacin. A special sonogram of your baby's heart (fetal echocardiogram) will be done once a day while you are on the indomethacin.

c) After you are discharged, you will need to stay at insert name of facility or hotel until you deliver. You will be at bed rest for one week. After the first week, you will be allowed to engage in light activity for the remainder of your pregnancy. You will return to the MOMS Center at least weekly so that your pregnancy can be monitored, the progress of your unborn baby followed closely by sonogram and your delivery planned. In addition to the usual examinations and tests that are done at a routine obstetrical visit, you will be assessed for the degree of discomfort you experienced after surgery, wound healing, and risks for premature labor and/or delivery. A complete obstetrical ultrasound will be done monthly.

d) If and when you are well enough to leave the hospital after the fetal surgery is performed, you will take a drug called "nifedipine" to prevent premature labor. You will take this medication for the duration of your pregnancy. If the nifedipine is not effective in preventing significant premature contractions or you are unable to tolerate the side effects of this medication, you will be placed on a terbutaline pump. A tiny needle is placed under the skin on your thigh to allow the pump to give small doses of terbutaline (another tocolytic drug) 24 hours a day. If placed on the terbutaline pump, you will remain on this medication for the duration of your pregnancy. A nurse will visit you regularly and you will have telephone access to a nurse and perinatologist (a doctor who monitors fetuses) who are supervising your progress.

e) When you are ready to deliver your baby (or when you have completed 36 weeks of your pregnancy), you will be readmitted to insert name of MOMS Center facility to deliver your baby by C-section. If you go into preterm labor before you have completed 34 weeks of your pregnancy and delivery is imminent, you will be given betamethasone or dexamethasone, steroid medications which will help your unborn baby's lungs mature. If you reach 37 weeks of pregnancy, an amniocentesis (removal by needle of a small amount of amniotic fluid for study) will be performed to assess the maturity of your baby's lungs. If they are not mature, delivery will be delayed for 5 to 7 days to allow for further lung development. The abdominal incision will be made in the same location used for the fetal surgery. The uterine incision used to deliver your baby will be in a location that is safest for your baby's delivery. It is probable that the uterine incision will be located in an area of your uterus that will not allow vaginal

deliveries for future pregnancies. Therefore, all of your future deliveries will probably be by C-section.

f) At delivery, your baby will be cared for at insert name of institution using standard postnatal therapies until he/she is fully recovered. That time period is variable and although it averages 7-14 days, it can be several weeks to several months. This means that you may have to stay in the insert name of area area for an extended amount of time or return home without your baby.

Surgery after birth group: If you are assigned to the standard postnatal surgery group, you will return home and will undergo routine obstetrical care in your home area. Your doctor will do monthly ultrasounds in addition to the usual prenatal care procedures. You will need to return to insert name of MOMS Center facility after you have completed 36 weeks of pregnancy, provided written medical clearance to travel (including to fly if indicated) is obtained from your obstetrician/perinatologist. Once you are at insert name of MOMS Center facility, a sample of amniotic fluid will be removed from your uterus using a small thin needle (amniocentesis) to find out if your unborn baby's lungs are mature enough for delivery. If they are not, delivery will be delayed 5 to 7 days to allow for further lung development. The baby will be delivered by C-section to prevent any further damage to the exposed spine. The baby's spina bifida defect will be closed as soon as possible after birth (usually within 48 hours).

C. FOLLOW-UP FOR BOTH GROUPS

Within one month of delivery, you will be asked to complete the three psychological tests you took before you were assigned to prenatal or postnatal surgery. After you go home, information about both your and your baby's health will be collected through medical reports, letters, and/or phone calls for several years. You will be asked to sign a separate consent form for follow-up. You will be contacted at least every three months by phone and questioned about any medical developments that might have taken place since you were last contacted for follow-up. You will be expected to return to insert name of MOMS Center when your baby is 12 months and 30 months of age. Your baby's development and medical status will be assessed at those visits. It is possible that a grant extension will be requested and granted and in that case another follow-up visit will take place after the 30 month visit.

IV. RISKS AND/OR DISCOMFORTS

There is the possibility that one procedure is better than the other for you and for your baby and the one you are assigned to may be the poorer of the two. Nearly all the risks and discomforts discussed below are based on information gained from over two hundred (200) fetal operations. There may be other unforeseen risks.

RISKS OF FETAL SURGERY

Maternal Risks

1. Wound infection after fetal surgery: This has occurred in less than 5% of cases and is usually superficial.
2. Chorioamnionitis (infection in the uterus): This has been a rare complication of the fetal surgery cases done for closure of spina bifida. If it does occur, preterm delivery and death of the baby may occur.

3. Amniotic fluid leak (leak of fluid from the uterus at the incision site): This has been a rare complication of fetal surgery done for closure of spina bifida, but if it does occur it is likely to result in too little amniotic fluid in the uterus. This is known as oligohydramnios. If it is diagnosed, you will probably be admitted to the hospital and treated with bed rest and IV (intravenous) fluids, maybe until delivery. A long-term lack of amniotic fluid can damage the unborn baby's lungs and could lead to death of the baby.
4. Prolonged hospitalization: It is possible that you will need to be hospitalized from the time of the fetal surgery until delivery. That could be as long as 20 weeks. This could have a serious effect on all members of your family.
5. Loss of future reproductive potential: An inability to have more babies should occur very rarely. One study of 45 women who had fetal surgery and no pre-existing fertility problems found that 32 of 35 who attempted pregnancy were able to conceive and deliver a full-term baby.
6. Necessity of C-section for future pregnancies: The fetal surgery is almost certain to make it necessary for your future deliveries to be by C-section.
7. Significant bleeding during fetal surgery or during delivery: All surgery carries a risk of blood loss. Bleeding that requires a blood transfusion after fetal surgery is extremely rare.
8. Side-effects from tocolytic agents: The side-effects should be no different for mothers whose babies have undergone fetal surgery for myelomeningocele than for mothers who experience preterm labor for any other reason. The possible side-effects of the drugs used in this study to prevent pre-term labor after fetal surgery are:

   Magnesium sulfate: flushing, sweating, muscle weakness, nausea and vomiting, blurred vision, excess fluid in the lungs leading to a need for oxygen

   Indomethacin: intestinal cramping, decreased amniotic fluid production

   Terbutaline: fast heart rate, nausea, constipation, headache, high blood sugar

   Nifedipine: low blood pressure, flushing, rash, headache
9. Complications and side-effects of general anesthesia and epidural analgesia: The fetal surgery procedure requires you to undergo an operation under general anesthesia that you would not have if you were assigned to the postnatal surgery group.

   General anesthesia: nausea and vomiting, aspiration (inhaling material into the lung), inability to maintain normal breathing requiring placement of a breathing tube into the trachea (windpipe)

   Epidural analgesia: headache, incomplete pain control, infection, hematoma formation (blood collecting around the tube), nerve injury, drug side-effects (itching, nausea and vomiting, inability to urinate, slow breathing, seizure, low blood pressure)
10. Death: This is extremely unlikely due to the intensive monitoring both during and after surgery and the fact that the physicians involved are very experienced obstetrical anesthesiologists and perinatologists. There has never been a maternal death at any of the centers participating in this study during or after any fetal surgical procedure.

Fetal Risks

1. Fetal/Neonatal death: To date, the perinatal death rate after fetal surgery for fetal myelomeningocele is approximately 5%.
2. Injury after surgery: It is possible that fetal surgery might increase injury to the baby by worsening the hydrocephalus before delivery. This has not been observed in any case so far.
3. Side-effects from tocolytic drugs: Significant narrowing of your baby's ductus arteriosus (blood vessel near the heart). If this occurs, this drug will be discontinued.
4. Prematurity: Fetal surgery can cause premature delivery resulting in severe problems associated with prematurity including but not limited to bleeding in the brain, cerebral palsy, difficulty with breathing because of immature lungs, severe infection, damage to the retina of the eyes, and an increased risk of infection of the premature intestines.
5. Chorioamniotic separation: This occurs in approximately 20% of cases of fetal surgery. MOMS Center doctors believe this to be due to tearing and separation of the membranes surrounding the baby during the opening of the uterus. This may lead to premature rupture of the membranes (PROM), amniotic band syndrome (strings of tissue that can wrap around and injure fingers, toes or limbs), and umbilical cord compression resulting in either poor fetal growth or fetal death. To date, there have been no known complications as a result of chorioamniotic separation. PROM has occurred with and without the presence of a chorioamniotic separation seen on ultrasound.
6. No improvement in your unborn baby's condition after fetal surgery for myelomeningocele.

Risks of Standard Postnatal Care

There are no risks to you. Risks to your baby are the progression of the Chiari II malformation prior to birth and subsequent need for placement of a shunt. Babies born with myelomeningocele may have a variety of medical complications including but not limited to breathing and swallowing difficulties, failure to thrive and grow well due to chronic illness, paralysis or weakness of the legs and or feet, and complications of prematurity including bleeding in the brain, difficulty with breathing due to immature lungs, and an increased risk of infection in the premature intestines.

V. TREATMENT AND COMPENSATION FOR INJURY

If you or your baby are injured as a result of taking part in this study, treatment will be available. The costs of such treatment may be covered by insert name of MOMS Center facility, depending on a number of factors. Insert name of facility does not usually provide any other form of compensation for injury. The National Institute of Child Health and Human Development will not provide care or coverage for care for injury suffered as a result of taking part in this study. For further information about this, you may call insert name of appropriate office at MOMS Center facility at insert phone number of office.

VI. BENEFITS

Either prenatal or postnatal repair of myelomeningocele may prove to be a more effective treatment for your baby's myelomeningocele. By "effective treatment", the doctors involved in this study mean that your baby may have the best chance of normal nerve function in the area affected by the spina bifida as well as the least number of short and long-term complications. After the study is completed and the data is analyzed, the doctors involved in the trial will learn whether one treatment is better than the other. This information is not presently known.

VII. ALTERNATIVES

You can decide not to participate in this study or terminate the pregnancy. You can decline fetal surgery but still allow study of your baby's outcome by signing a separate consent form. In that case, you can choose to return to your referring doctor and hospital or be cared for at insert name of MOMS Center facility.

VIII. FINANCIAL CONSIDERATIONS

If you do choose to take part in this study, there will be no additional costs for prenatal care beyond those you would normally have. If you are in the fetal surgery group, the travel, meal and lodging costs for you and a relative or friend will be covered until delivery and after delivery until you take your baby home. If you are in the postnatal surgery group, your travel back to the center will be covered, as well as food and accommodation before and after delivery until your baby is able to go home with you. In addition, the cost of all medical care associated with the study not covered by your insurance will be covered by the study. For both the prenatal and postnatal surgery groups, the cost of returning with your baby at one year and two and a half years will also be covered by the study. Meals and lodging will be covered as well.

IX. COMPENSATION

You will not be compensated (paid) for your participation in this study.

X. RIGHT TO WITHDRAW FROM THE STUDY

Your participation in this research study is voluntary. You may decide not to begin or to stop your participation in this study at any time.

XI. CONFIDENTIALITY OF MEDICAL AND RESEARCH RECORDS

Participation in this study will cause some loss of privacy. However, all of your records and your baby's records will be handled as confidentially as possible. The details of what happens to you and your baby will be recorded by the doctors participating in the study. If you do decide to take part in the trial, your medical data collected for this study will be sent to the George Washington Biostatistics Center and put into a central database consisting of information from all of the participants in the study. The medical data sent to the central database will not include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Your information in the database will only be used

for statistical analysis and may appear in scientific publications. You will not be identified in any publications. Authorized staff from the National Institute of Child Health and Human Development may review your medical data to evaluate the progress of the study.

To help us protect your privacy, we have obtained a certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

XII. QUESTIONS

The above information has been explained to you by insert name of doctor and members of the MOMS Center. They have answered your questions concerning participation in the study. You may reach them at any time at insert name of MOMS Center facility or by calling insert name of appropriate contact person at insert phone number of appropriate contact person.

XIII. CONSENT

Participation in this study is voluntary and you may withdraw at any time. Declining to participate or withdrawing from the study will not jeopardize your treatment or your baby's treatment. The investigators may end your participation in the study prior to undergoing surgery if they deem it medically advisable.

You will be given a copy of this consent form to keep.

If you wish to participate you should sign below.

_____ _____
Mother's signature Date

_____ _____
Father's signature (if appropriate) Date

_____ _____
Person obtaining consent Date

B.3 SAMPLE STUDY FOLLOW-UP CONSENT FORM

Consent for Follow-up by the Management of Myelomeningocele Study (MOMS)

I. PURPOSE AND BACKGROUND

The National Institute of Child Health and Human Development (NICHD) has funded a multicenter study to investigate whether closure of myelomeningocele (spina bifida) while the baby is in the mother's womb (prenatal surgery) is better for the baby's outcome than closure after the baby is born (postnatal surgery). This consent applies to follow-up studies which will be done to gather additional data to be used to determine if either surgery is more safe and/or effective.

II. PROCEDURES

If you agree to participate in this study, the following will occur:

1. After your child is discharged from the hospital, you will be contacted at least every three months for two and a half years so that study staff can obtain updates of both your and your child's condition.
2. Your child will undergo two follow-up evaluations at insert name of MOMS center facility. He/she will be evaluated at one year of age and two and a half years of age. The one-year evaluation will include an MRI of the head and spine and both the one-year and two and a half year evaluation will include a physical examination and developmental testing. Special testing of the kidneys and bladder (standard in the care of babies with spina bifida) will be done at the two and a half year visit if the testing has not been done as part of your child's routine follow-up care in the previous year.
3. At both the one-year and two and a half year follow-up visits, you and your partner will again complete the three psychological tests which you completed previously.
4. It is possible that, if additional funding is made available through a grant extension, you will be contacted about attending an additional follow-up visit beyond the one currently planned at two and a half years.

III. RISK/DISCOMFORTS

1. Some of the questions asked may make you uncomfortable or upset.
2. Some of the testing may upset your child. However, all of the planned tests are part of the routine care of a child with spina bifida.
3. As with participation in any research study, you may lose some privacy. However, your medical records will be handled as confidentially as possible. No individual names or other identifiers such as birthday or social security number will be used in any reports or publications that may result from this study.
4. You will be required to return to the MOMS Center for follow-up testing and this may be inconvenient for you and your family.

IV. BENEFITS

There is no direct benefit to you from participating in the follow-up portion of this study. However, you may receive advice on management of the problems which affect babies with myelomeningocele. The information that you provide may provide essential information as to whether prenatal or postnatal surgery provides a better outcome for babies with myelomeningocele.

V. COSTS

If you do choose to participate in the follow-up portion of this study, there will be no additional costs to you. All evaluations done as part of the follow-up portion of this study not covered by your insurance will be covered by the study. The costs of travel to insert name of facility for you, your partner and your baby will be covered by the study, as will costs for meals and lodging.

VI. COMPENSATION

You will not be compensated (paid) for your participation in the follow-up portion of this study.

VII. CONFIDENTIALITY OF MEDICAL AND RESEARCH RECORDS

You have the right to privacy. All information obtained from this research that can be identified with you will remain as confidential as possible. Representatives of governmental agencies may review and photocopy your medical and research records to assure the quality of the information being used in the research.

To help us protect your privacy, we have obtained a certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

VIII. QUESTIONS

You have the right to have all of your questions about participation in the follow-up portion of this study answered. You should direct any questions to insert name of study doctor and or nurse. If you do not wish to do this you can contact insert name of appropriate office at MOMS center facility at insert phone number of appropriate office at MOMS center facility.

IX. CONSENT

You will be given a copy of this consent form to keep.

Participation in research is voluntary. You are free to decline to be in the study. Your decision as to whether or not to participate will have no influence on your present or future status as a patient at insert name of MOMS center facility.

If you agree to participate, sign below.

_____	_____
Mother's signature	Date
_____	_____
Father's signature	Date
_____	_____
Signature of witness	Date
_____	_____
Signature of person obtaining consent	Date

APPENDIX C. PRENATAL SURGERY PROCEDURE

A combination of general and epidural anesthesia is used because of evidence suggesting that this combination is superior to either individually in preventing unwanted uterine contractions.58 The indwelling epidural catheter also enables administration of continuous postoperative analgesics. The gravid uterus will be exposed via a low transverse laparotomy incision and exteriorized. A vertical skin incision will be used in obese patients (BMI>30) or those with a previous vertical skin scar. The fetus and placenta are then located by ultrasound and the hysterotomy location chosen by the primary surgeon. Initial uterine entry is accomplished through a 1-2 cm hysterotomy. The foot plate of a US Surgical CS-57 autostapling device is passed into the uterine cavity. The stapler is examined manually and with color Doppler ultrasonography to exclude the presence of fetal tissue, and then used to create a 6-8 cm uterine incision. The fetus is directly visualized and manually positioned within the uterus such that the myelomeningocele sac is in the center of the hysterotomy. The fetus is given an injection of fentanyl. During the procedure the fetal heartbeat is monitored by continuous electronic fetal monitoring (EFM).

The myelomeningocele is closed in a standardized manner under magnification regardless of the gestational age. The neural placode is sharply dissected from surrounding tissue and allowed to drop into the spinal canal. The dura is then identified, reflected over the placode and then closed using a fine running suture. If there is insufficient dura for closure, Duragen may be substituted. If it is not possible to obtain skin closure, relaxing incisions are made. Finally, the skin is mobilized and closed using a fine running suture.

The uterus is closed in two layers. The first layer incorporates the absorbable polyglycolic acid staples left by the autostapling device. As the last stitches of this layer are placed, warmed Ringer's lactate, mixed with 500 mg of Nafcillin or vancomycin, is added to the uterus until the amniotic fluid index is normal. Finally, an imbricating layer of suture is placed. The abdominal fascial layer and dermis are closed in routine fashion.

REFERENCES

1. Current Trends in Economic Burden of Spina Bifida-United States, 1980-1990. http://www.cdc.gov/mmwr/preview/mmwrhtml/00001378.htm. Accessed on Feb 1, 2001.
2. Shurtleff DB, Luthy DA, Nyberg DA, Benedetti TJ, Mack LA. Meningocele: Management in utero and postnatum. Ciba Foundation Symp 181:270-86, 1994.
3. Hunt GM. The median survival time in open spina bifida. Dev Med Child Neurol 39:568, 1997.
4. Manning SM, Jennings R, Madsen JR. Pathophysiology, prevention and potential treatment of neural tube defects. Mental Retardation and Developmental Disabilities Research Reviews 6:6-14, 2000.
5. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural tube defects. N Engl J Med 341(20):1509-19, 1999.
6. Drennan JC. Foot deformities in myelomeningocele. In Thilos HS (Ed) Instructional Course Lectures. American Academy of Orthopedic Surgeons, Park Ridge, Illinois, 1991.
7. Cochrane DD, Wilson RD, Steinbok P, Farquharson DF, Irwin B, Irvine B, Chambers K. Prenatal spinal evaluation and functional outcome of patients born with myelomeningocele: information for improved prenatal counseling and outcome prediction. Fetal Diagn Ther 11:159-16, 1996.
8. Cass AS, Luxenburg M, Johnson CF, Gleich P. Incidence of urinary tract complications with myelomeningocele. Urology 25: 374-378, 1995.
9. Fletcher JM, Dennis M, Northrup H. Hydrocephalus, in Yeates KO, Ris MD and Taylor HG (eds): Pediatric Neuropsychology: Research, Theory and Practice. Guilford Press Therapy in Pediatrics, New York, 2000.
10. Yeates KO, Enrile, Loss N, Blumenstein E, Delis C. Verbal learning and memory in children with myelomeningocele. J Pediatr Psychol 20:801-815, 1995.
11. Lavigne J, Faier-Routman J. Psychological adjustment to pediatric physical disorders: A meta-analytic review. J Pediatr Psychol 17:133-57, 1992.
12. Villablanca JR, Hovda DA. Developmental neuroplasticity in a model of cerebral hemispherectomy and stroke. Neuroscience 95(3):625-637, 2000.
13. Michejda M. Intrauterine treatment of spina bifida: primate model. Z Kinderchir 39:259-61, 1984.
14. Heffez DS, Aryanpur J, Hutchins GM, Freeman JM. The paralysis associated with myelomeningocele: clinical and experimental data implicating a preventable spinal cord injury. Neurosurgery 26:987-992, 1990.
15. Heffez DS, Aryanpur J, Rotellini NA, Hutchins GM, Freeman JM. Intrauterine repair of experimental surgically created dysraphism. Neurosurgery 32:1005-1010, 1993.
16. Meuli M, Meuli-Simmen C, Hutchins GM, et al. In utero surgery rescues neurological function at birth in sheep with spina bifida. Nat Med 1:342-7, 1995.
17. Meuli M, Meuli-Simmen C, Yingling CD, et al. Creation of myelomeningocele in utero: a model of functional damage from spinal cord exposure in fetal sheep [see comments]. J Pediatr Surg 30:1028-32; discussion 1032-3, 1995.

18. Paek VW, Farmer DL, Wilkinson CC et al. Hindbrain herniation develops in surgically created myelomeningocele but is absent after repair in fetal lambs. Am J Obstet Gyn. 183: 1119-1123, 2000.

19. Tulipan N, Bruner JP, Hernanz-Schulman M, Lowe LH, Walsh WF, Nickolaus D, Oakes WJ. The effect of intrauterine myelomeningocele repair on central nervous system structure and neurologic function. Pediatr Neurosurg 31:183-8, 1999.

20. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AW. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. JAMA 282:1826-31, 1999.

21. Bruner J, et al. Fetal Surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. JAMA 282: 1819-25, 1999.

22. Longaker MT, Golbus MS, Filly RA, Rosen MA, Chang SW, Harrison MW. Maternal outcome after open fetal surgery. A review of the first 17 human cases. JAMA 265:737-741, 1991.

23. Harrison MR. Fetal surgery. West J Med 159:341-349, 1993.

24. Farrell JA, Albanese CT, Kilpatrick S, Jennings RW, Harrison MR. Maternal fertility is unaffected after fetal surgery. Fetal Diag Ther 14:190-192, 1999.

25. Simpson JL. Fetal surgery for myelomeningocele: Promise, progress, and problems. JAMA 282(12):1873-1874, 1999. Editorial.

26. Wei LJ. An application of an urn model to the design of sequential controlled trials. J Am Stat Assoc 73:559-563, 1978.

27. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. J of Person Assess 49:71-75, 1985.

28. Pavot W, Diener E, Colvin R, Sandvik E. Further validation of the satisfaction with life scale: evidence for the cross-method convergence of well-being measures. J of Person Assess 57:149-16, 1991.

29. Scheier MF, Carver CS. Optimism, coping and health: assessment and implications of generalized outcome expectancies. Health Psychol 4(3):219-247, 1985.

30. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch of Gen Psych 4:561-571, 1961.

31. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psych Rev 17(3):277-285, 1998.

32. Luthy DA, Wardinsky T, Shurtleff DB, Hollenbach K, Hickok DE, Nyberg DA, Benedetti T. Cesarean section before the onset of labor and subsequent motor function in infants with myelomeningocele diagnosed antenatally. N Engl J Med. 342(10): 662-666, 1993.

33. Kuller JA, Katz VL, Wells SR. Wright LN, McMahon MJ. Cesarean delivery for fetal malformation. Obstet Gynecol Surv 51:371-375, 1996.

34. Palisano R, Rosenbaum, Walter S. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol, 39: 214-223, 1997.

35. Daniels L, Worthingham C. Muscle testing: Techniques of Manual Examination, 5th Edition. WB Saunders, Philadelphia PA, 1986.

36. Kendall FP, McCreary EK, Provance PG (eds). Muscles: Testing and Function, 4" Edition. Williams and Wilkins, Baltimore MD, 1999.

37. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 3rd ed. St. Louis: Mosby, 1996.

38. Casagrande JT, Pike MC, Smith PG. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. Biometrics 34: 483-486, 1978.

39. O'Brien PC. Procedures for comparing samples with multiple endpoints. Biometrics 40: 1079-1087, 1984.

40. Whitehead J. Sample size calculations for ordered categorical data. Statistics in Medicine 12: 2257-2271, 1993.

41. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika, 1983;70:659-63.

42. Bolland, K. and Whitehead, J. Formal approaches to safety monitoring of clinical trials in life-threatening conditions. Statistics in Medicine 19:2899-2917, 2001.

43. Armitage, P. Interim Analysis of Clinical Trials. Statistics in Medicine 10:925-937, 1991.

44. Newell DJ. Intention-to-treat analysis: Implications for quantitative and qualitative research. International Journal of Epidemiology 21:837-841, 1992.

45. Lachin J. Statistical considerations in the intent-to-treat principle. Controlled Clinical Trials 21:167-189, 2000.

46. Wei LJ and Lachin JM. Two-sample asymptotically distribution-free tests for incomplete multivariate observations. Journal of the American Statistical Association 79:653-661, 1984.

47. Agresti A. Categorical Data Analysis. New York; John Wiley & Sons, 1990.

48. Kalbfleisch JD and Prentice RL. The Statistical Analysis of Failure Time Data. New York: John Wiley, 1980.

49. Harrington DP and Fleming T. A class of rank test procedures for censored survival data. Biometrika 69:553-566, 1982.

50. Andersen PK, Borgan O, Gill R and Keiding N. Statistical Models Based on Counting Processes. New York. Springer-Verlag 1993.

51. Diggle PJ, Liang K-Y, Zeger SL. Analysis of Longitudinal Data. New York; Oxford University Press, 1994.

52. Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. Biometrics 42: 805-820, 1986.

53. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 38:963-974, 1982.

54. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 73:13-22, 1986.

55. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42:121-130, 1986.

56. Canner PL. Covariate adjustment of treatment effects in clinical trials. Controlled Clinical Trials 12:359-366, 1991.

57. Snee RD. Validation of regression methods. Technometrics 19:415-428, 1977.

58. Thorp JA, Meyer BA, Cohen GR, Yeast JD, Hu D. Epidural analgesia in labor and cesarean delivery for dystocia. Obstet Gynecol Surv 49:362-9, 1994.