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3 **Optimizing Management of the Second Stage of Labor:**
4 **a Multicenter Trial**

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6 **“OMSS”**

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9 **PROTOCOL**

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11 **Version 5**

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A. PROTOCOL SUMMARY

Optimizing Management of the Second Stage of Labor (OMSS): a Multicenter Trial

Objective: To assess the effectiveness of immediate pushing at complete cervical dilation in nulliparous women on: 1) rate of spontaneous vaginal delivery, 2) composite neonatal morbidity, and 3) maternal pelvic floor dysfunction.

Organization:

Clinical Centers: Washington University in St. Louis School of Medicine; University of Alabama in Birmingham; Oregon Health and Sciences University; University of Pennsylvania, Missouri Baptist Medical Center, Pennsylvania Hospital

Study and Data Coordinating Center: Washington University in St. Louis School of Medicine

Steering Committee: Dr. Graham Colditz (chair), PI/PDs, each of the center PIs, Dr Richter

Data Safety and Monitoring Board: Dr. Rouse (chair), Dr. Klebanoff, Dr. Ananth

Design:

Type: Randomized clinical trial

Inclusion criteria:

1. Singleton term pregnancy: gestational age ≥ 37 weeks
2. Nulliparous
3. Neuraxial anesthesia
4. Ability to give informed consent

Exclusion criteria:

1. Preterm: gestational age < 37 weeks
2. Multiparous
3. Multiple gestations
4. Non-reassuring fetal heart rate tracing at randomization
5. Contraindication to vaginal delivery including: non-vertex presentation, placenta previa, prior classical cesarean, etc.
6. Inadequate neuraxial anesthesia
7. Pregnancy complications requiring expedited delivery e.g. severe preeclampsia, abruption, maternal cardiac disease, active hepatitis, HIV infection, chorioamnionitis
8. Fetal head visible at the introitus at complete cervical dilation
9. Known major fetal anomaly
10. Intrauterine fetal death

Allocation: Block randomization, stratified by study site

Stratification: Study center

Sample size: Assumptions

1. Power=90% for primary outcome
2. Type 1 error=5% (2-sided)
3. Primary outcome
 - Delayed pushing event rate (based on preliminary data)
 - Nulliparous – 72%
 - Anticipated 5% absolute difference in SVD with immediate
 - Anticipated 2% reduction in neonatal composite morbidity

Total=3184

Delayed=1592, Immediate=1592

Interventions:

Immediate pushing: Immediate maternal pushing

Delayed pushing: Delay pushing for 60 minutes from first documentation of complete cervical dilation

Analysis:

Primary: Intention-to-treat

Secondary: Prespecified subgroup and adjusted analyses

Management Protocols:

Immediate pushing:

- o Initiation of pushing at first documentation of complete dilation
- o Pushing technique and frequency/pace according to local and practitioner standard

Delayed pushing:

- o Pushing delayed for 60 minutes after complete dilation
- o Initiation if clinical indication prior to 60 minutes; push if irresistible urge or clinically indicated
- o Pushing technique and frequency/pace according to local and practitioner standard

Outcome Measures:

Primary:

Secondary:

Spontaneous vaginal delivery

1. Cesarean delivery
2. Operative vaginal delivery
3. Composite neonatal morbidity (neonatal death, major neonatal injury, umbilical artery cord pH < 7.1 , composite morbidities)
4. Overt perineal laceration (2nd, 3rd, 4th degree)
5. Occult levator ani injury (defined as interruption in levator ani muscle on 3D transperineal ultrasound 1-5 days postpartum)
6. Urinary incontinence, fecal incontinence, pelvic organ prolapse
7. Postpartum hemorrhage, chorioamnionitis, endometritis
8. Second stage and active pushing durations

Pelvic Floor Assessment

Inclusion criteria: Enrollment in the trial

Assessment:

- 1-5d postpartum, 3D perineal US, QOL surveys
- 4-8w postpartum, 3D US, POPQ, symptoms & QOL surveys
- 5-7mo postpartum, 3D US, POPQ, symptoms & QOL surveys

Timetable:

Recruitment: 6 months to 54 months

Data Collection: 6 months to 54 months

Interim Analysis: (i) N=1,592 (50%), (ii) N=2,388 (75%)

Final analysis: N=3184

B. INTRODUCTION

B1. Study Abstract

Over three million pregnant women labor and give birth in the United States every year. Despite the frequency of this event, many aspects of labor management lack evidence. The second stage of labor, defined as the interval from complete cervical dilation through delivery of the fetus, is the most physiologically demanding period of labor for both the mother and the fetus. Despite the huge impact labor management can have on mode of delivery and neonatal and maternal morbidities, the optimal technique for managing maternal pushing during the second stage of labor is unknown. The two most common approaches involve either allowing for spontaneous descent (delayed pushing) or initiating pushing with uterine contractions once complete cervical dilation occurs (immediate pushing). Prior studies comparing these approaches reported results that are contradictory with regard to benefit and harm to the neonate and mother. Despite these data, delayed pushing gained wide spread use with a perception that it improves rates of vaginal delivery and reduces morbidities. By contrast, our recent meta-analysis demonstrated that among high-quality trials, delayed pushing did not improve the spontaneous vaginal delivery rate, but prolonged second stage duration. Notably, the largest trial evaluated outcome measures that are obsolete in contemporary obstetrics in the United States, such as use of mid-pelvic rotational forceps. Results of our large observational study indicated that selection to delayed pushing is associated with worse labor outcomes than immediate pushing. The lack of a modern, large, well-controlled, randomized clinical trial to address this question has led to uncertainty as to which technique for maternal pushing in the second stage of labor optimizes outcomes. In addition, effects of immediate versus delayed pushing on risk of maternal pelvic floor injury remain unknown. Given that approximately 11,000 women labor and deliver daily in the United States, there is an urgent need to fill this important clinical knowledge gap and provide high-quality evidence to inform contemporary obstetric management of the second stage of labor.

This is a large, multicenter, randomized clinical trial of immediate versus delayed pushing for nulliparous women in labor at term reaching complete cervical dilation. We estimate that randomizing a total of **3184** women will provide adequate statistical power to detect meaningful differences in the primary and secondary outcomes.

B2. Hypotheses and Specific Aims

Our central hypothesis is that immediate pushing in the second stage of labor increases spontaneous vaginal delivery, shortens duration of the second stage, and reduces adverse neonatal and maternal outcomes in nulliparous women. We will pursue the following specific aims:

1) **Primary Aim:** Assess the effectiveness of immediate pushing at complete cervical dilation on the rate of spontaneous vaginal delivery in nulliparous women. *Hypothesis: Nulliparous women will have an increase in spontaneous vaginal delivery rates with immediate, as compared to delayed, pushing.*

2) **Secondary Aims:**

- i. Determine the effect of immediate pushing on the rate of neonatal composite morbidity. *Hypothesis: Immediate pushing will reduce the rate of neonatal composite morbidity, defined as one or more of: neonatal death, major neonatal injury, umbilical cord arterial acidosis, suspected neonatal sepsis, respiratory distress, transient tachypnea, meconium aspiration with pulmonary hypertension, hypoxic-ischemic encephalopathy, hypoglycemia, and need for hypothermia treatment.*
- ii. Determine the impact of immediate versus delayed pushing on objective and subjective measures of maternal pelvic floor morbidity. *Hypothesis: Immediate pushing will be associated with a reduction in the rate of acute levator ani and anal sphincter muscle injury, and lower rates of pelvic floor disorders identified on subjective and objective clinical assessments.*

B3. Purpose of the Study Protocol

This protocol describes the background, design and organization of the trial. It is part of the manual of operations and serves as a written agreement between the study investigators. It is reviewed and approved by the Steering Committee, Data Safety and Monitoring Board and the Institutional Review Board of each participating center. Any changes to the protocol during the study will require approval by the Steering Committee.

C. BACKGROUND

Women labor and deliver over three million times per year in the U.S. [1] Labor, the process by which the gravid uterus contracts regularly, causing the cervix to dilate and the fetus to descend through the birth canal to result in delivery of the infant and subsequently the placenta, is divided into three stages. In the first stage, uterine contractions increase in frequency, progressively dilating the cervix until it reaches 10 centimeters (or maximum) in diameter. The second stage begins when the cervix is maximally dilated and ends with delivery of the infant. The third stage follows infant birth and yields delivery of the placenta. Of the stages, the second stage of labor is the most physiologically demanding and prone to morbidities for both the mother and infant.

C1. Labor and Delivery: Maternal and Neonatal Morbidity

C1-1. Physiologic alterations and morbidity risk: Although most women of child-bearing age are healthy, there is risk of significant maternal morbidity and even mortality during the labor and delivery process. Pregnancy is characterized by a 50% increase in cardiac output and effective circulating blood volume. At the onset of labor, and then progressively during the first stage of labor as uterine contraction frequency and intensity increase, the cardiovascular system is further challenged by a 300-500 mL autotransfusion with each contraction, typically occurring every 2-3 minutes. In the second stage, these cardiovascular demands are further challenged by maternal expulsive efforts, generating significant intra-abdominal and thoracic pressures and limiting blood delivery to the uterus and placenta. Further, as demonstrated by several large cohort studies, the risks of maternal infection, hemorrhage, and laceration increase with each hour of second stage duration [2-4].

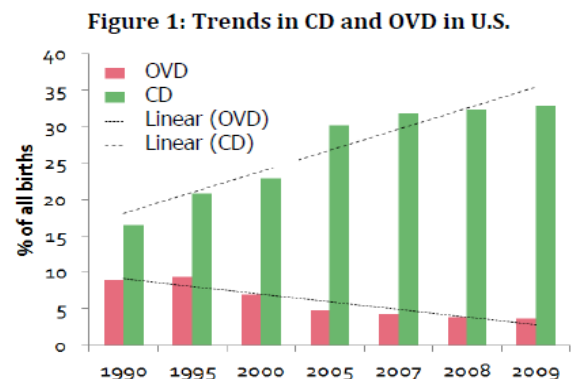
C1-2. Neonatal morbidities: Fetal gas exchange is completely reliant on maternal blood flow and delivery of oxygenated blood to the placenta. It is not surprising then, that otherwise healthy term infants born from the second stage of labor have a lower pH at birth than those delivered by cesarean during the first stage of labor[5]. Thus, the risks of neonatal acidemia (low pH and elevated base excess) and neonatal depression, as well as significant morbidities requiring intensive care, increase with increasing second stage duration [3, 6, 7].

C1-3. Pelvic floor injuries: Up to 25% of women who deliver suffer from pelvic floor injuries [8, 9], specifically injury to the levator ani muscle (LAM)[10]. LAM injury is strongly associated with fecal incontinence and pelvic organ prolapse years after delivery [11, 12], which can negatively affect quality of life [13]. Although clinically identified perineal injuries (particularly 3rd and 4th degree obstetric lacerations) indicate LAM injury and risk for future morbidity, many women apparently have occult injuries that lead to incontinence in their later years. Heilbrun et al demonstrated that primiparous women with LAM injury, identified by post-natal imaging with magnetic resonance imaging (MRI), were significantly more likely to suffer from fecal incontinence than those without evidence of acute injury (35.0% vs 10.2%, $p=0.006$)[11]. Because many LAM injuries go undetected, the labor management strategies, and specifically those for the second stage, that are associated with an increase in risk of LAM injuries remain unknown. What has been highlighted is that for women who reach the second stage of labor, cesarean does not reduce the risk of pelvic floor injury, and specifically injury to the LAM [10]. Thus, the association between labor management strategies and LAM injury, risk of fecal and urinary incontinence, risk of prolapse, and quality of life needs to be investigated.

C2. Promoting Optimum Labor Outcomes

C2-1. Neonatal and maternal morbidities from operative deliveries: Operative delivery (defined as cesarean or operative vaginal delivery), which now occurs in 37% of births, is associated with increased risk of most labor- and delivery-related complications, including maternal hemorrhage, infection, thromboembolism, severe perineal lacerations, and even death; as well as neonatal depressed Apgar scores, acidemia, birth trauma, and intensive care admissions[14]. Further, once a cesarean is performed, the risk of delivery by cesarean for future pregnancies is dramatically elevated [15].

C2-2. Increasing the rate of spontaneous vaginal deliveries: The 100% increase in the cesarean rate in the last 30 years (from 16.5% in 1980 to 32.8% in 2010)[1] has been multifactorial,



276 meaning that reduction will not come from a single strategy. To increase the rate of spontaneous vaginal
277 delivery, and reduce maternal and neonatal morbidity, both operative vaginal delivery and cesarean must be
278 reduced. In modern obstetrics, these two modes of delivery are *competing risks*, best demonstrated by the
279 concomitant temporal trends in operative vaginal delivery (OVD) and cesarean (CD) (**Fig. 1**) [1].

280 C2-3. Optimizing management of the second stage of labor: Historically, when the second stage of labor began
281 (at 10 centimeters cervical dilation), women involuntarily pushed to deliver their infants. With the advent of
282 regional anesthesia (which is used by more than 85% of women delivering in a hospital setting), successfully
283 blunting maternal labor pain but simultaneously blunting the reflexive urge to push, management of the second
284 stage of labor became care-giver driven. Thus, the question arose as to which strategy would result in the best
285 outcomes: 1) immediate pushing – coaching maternal voluntary pushing efforts – at the time of complete
286 dilation, or 2) delayed pushing – allowing for a period of time between maximal cervical dilation and initiation of
287 pushing to allow infant descent by uterine contractions alone. Several studies were performed to address this
288 question. The largest randomized trial, of 1862 nulliparous women, was reported in 2000. This study showed
289 a reduction in composite birth morbidity associated with delayed pushing [16]. Similarly, a meta-analysis
290 reported in 2008 suggested that, compared with immediate pushing, delayed pushing was associated with
291 increased spontaneous vaginal deliveries, decreased operative vaginal deliveries, and decreased duration of
292 active pushing [17]. Given these findings, the Association of Women's Health, Obstetric and Neonatal Nurses
293 published guidelines in 2008 recommending delayed pushing in the second stage of labor unless
294 contraindicated by maternal or fetal condition.

295 C2-4. Limitations of evidence to guide contemporary obstetric practice: The above studies have limited
296 applicability to current obstetrical practice. For example, the significant findings in the largest trial were driven
297 by a reduction in mid-pelvic forceps deliveries, which are obsolete in modern obstetric practice in the U.S. [18]
298 Because the rate of use of mid-pelvic forceps was so high in the trial, as was the typical practice 20 years ago,
299 we attempted to conduct a secondary analysis among those who did not undergo mid-pelvic forceps delivery,
300 but we found that these data were only 55% powered to detect whether delayed versus immediate pushing is
301 superior. Thus, optimal management of the second stage cannot be determined from secondary analysis of
302 this existing data. The current uncertainty results in an estimated 50% of practitioners using delayed pushing
303 and the other 50% using immediate. This means that half of all practitioners are employing a strategy that is
304 potentially contributing to increased operative (both cesarean and operative vaginal) deliveries, neonatal
305 morbidity, and maternal pelvic floor dysfunction. This proposal is for a much-needed multicenter, simple,
306 randomized clinical trial that is powered to identify the optimal management strategy for the second stage of
307 labor.

309 **C3. Public Health Impact**

310 The public health impact of the decrease in rate of spontaneous vaginal deliveries has been significant, and
311 the causes are multi-factorial [1, 15]. A reduction in the national rate of cesarean by reducing iatrogenic
312 cesarean deliveries will require a series of discoveries, each contributing evidence for improved labor and
313 delivery care. The current proposal, optimizing management of the second stage of labor, assumes an
314 increase in the rate of spontaneous vaginal delivery by 5% or greater in nulliparous women (from 72% to 77%)
315 due to immediate pushing. At face value this may appear modest and inconsequential. However, this
316 represents approximately 5% absolute decrease in operative deliveries (combined cesarean and operative
317 vaginal, from 28% to 23%). In addition, the proposed trial will be conducted at six labor and delivery units, with
318 a wide diversity of providers and patients to optimize generalizability. Considering the number of nulliparous
319 women who labor and deliver a live born infant each year (40% of the over 3 million deliveries in the U.S.
320 annually), that cesarean delivery is the most common major surgical procedure performed in women, and that
321 operative deliveries are linked directly and indirectly to increases in virtually all child-birth related morbidities, a
322 5% reduction would result in approximately 12,000 fewer second-stage cesareans and 48,000 fewer operative
323 vaginal deliveries performed[1], with an estimated cost savings of approximately \$200 million each year [1, 19].

D. STUDY DESIGN

D1. Design Overview

This is a multicenter randomized trial of nulliparous women to compare the effectiveness of immediate and delayed pushing in the second stage of labor. We aim to test the central hypothesis that immediate pushing in the second stage of labor increases spontaneous vaginal delivery, shortens duration of the second stage, and reduces adverse neonatal and maternal outcomes. With the limitations and inapplicability of the existing data to modern practice and the uncertain effect of immediate pushing on spontaneous vaginal delivery, we estimated our sample size and plan our data analysis based on two-tailed tests. This will ensure that we identify the optimal management strategy for the second stage that increases spontaneous vaginal delivery, irrespective of the direction of our findings. The proposed trial will fill an important knowledge gap and provide high-quality, generalizable evidence to help women and their physicians decide on a birthing plan that maximizes spontaneous vaginal delivery and minimizes maternal and neonatal morbidity.

We chose a randomized controlled trial, the 'gold standard' of clinical research design, with the goal of obtaining the highest quality evidence to inform clinical practice. Randomly allocating subjects to different interventions minimizes selection bias and results in groups that are comparable with regards to important confounding variables, both measured and unmeasured. Additionally, the broad inclusion criteria, simplicity in relationship of the interventions to current practice, and the multicenter design with regional representation and practice diversity increase generalizability and direct application of the findings.

We will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines wherever appropriate in the conduct and reporting of this trial [20]. We will use computer-generated random sequences, stratified by study site, to assign participants to the two interventions. Labor management will be similar in the two groups except for the timing of maternal pushing effort. Analysis will follow the intention-to-treat principle. The use of broad inclusion criteria and intention-to-treat analysis will allow a more conservative estimate of differences in outcomes between the two strategies and allow a better estimate of effectiveness and public health implications of practice change than would pure estimate of efficacy alone [21].

D2. Study Sites and Populations

1. Washington University Medical Center — Coordinating center (PI/PD-Cahill/Tuuli): The obstetrical service at WUMC delivers babies for approximately 4000 women annually. WUMC is a tertiary care hospital and draws all ethnic groups typical of a large urban referral hospital. Approximately 55% are Caucasian, 30% African American, and 15% of other racial groups. Patients are largely managed by resident physicians under the supervision of faculty of the Washington School of Medicine (WUSM) and non-academic community OB/GYN physicians. Providers are private practice generalists, academic general OB/GYNs, and maternal-fetal medicine (MFM) specialists.

Sub site: Missouri Baptist Medical Center is a private hospital affiliated with WUSM. The obstetric service delivers 4000 women annually, predominantly by private physicians. Drs Cahill and Tuuli and other members of the WUMC MFM division provide 24/7 MFM coverage for the Missouri Baptist Medical Center.

2. University of Alabama at Birmingham (Site PI-Tita): UAB Hospital is the major perinatal referral facility for Alabama. Approximately 4200 women (53% African American, 25% Caucasian, 20% Hispanic, and 2% other ethnic groups) are delivered annually in the Women and Infants Center. Provider mix includes MFM specialists with oversight of residents and private-practice general OB/GYN physicians.

3. Hospital of the University of Pennsylvania (Site PI-Srinivas): The obstetrical service at Penn delivers approximately 4100 women per year. Penn is an urban tertiary care hospital with a diverse population. Patients are managed by faculty of the Penn School of Medicine. Provider mix includes resident physicians under the supervision of MFM or academic generalists, private practice OB/GYNs, family practitioners, and nurse-midwives.

Sub site: Pennsylvania Hospital is a close affiliate of Penn. The obstetric unit is staffed by both private obstetricians and midwives. Of the 4600 – 5000 deliveries performed annually, 4000 – 4500 are performed by private physicians and 300 – 600 by midwives.

4. Oregon Health & Science University (Site PI-Caughey): The Labor and Delivery Unit at OHSU delivers approximately 2700 women per year. OHSU is a tertiary care hospital and the only academic medical center in Oregon. Patients from a wide range of socioeconomic backgrounds are managed by a diverse group of practitioners, including resident physicians and midwives with oversight from general OB/GYN physicians, family medicine physicians, and MFM specialists.

D3. Inclusion and exclusion criteria

We will use broad inclusion criteria to ensure generalizability of our results. Exclusion criteria will be limited to conditions for which vaginal delivery is contraindicated or expedited delivery is required (**Table 1**).

Table 1: Inclusion and exclusion criteria

Inclusion criteria
<ul style="list-style-type: none"> • Singleton term pregnancy: gestational age $\geq 37^{0/7}$ weeks by best obstetrical estimate <ul style="list-style-type: none"> • A twin pregnancy reduced to a singleton (spontaneously or therapeutically) before $14^{0/7}$ is acceptable • Nulliparous women (a pregnancy that ended before $20^{0/7}$ weeks is acceptable) • Neuraxial anesthesia: epidural or combined epidural-spinal anesthesia • Ability to give informed consent
Exclusion criteria (rationale)
<ul style="list-style-type: none"> • Preterm: gestational age < 37 weeks (preterm infants have an <i>a priori</i> risk for adverse outcomes, which is driven more by gestational age than the timing of maternal pushing in the second stage) • Multiple gestation (incidence of multiple gestation is small and there are unique delivery considerations) • Multiparous women • Non-reassuring fetal heart rate tracing at randomization (will be an indication for expedited delivery) • Contraindication to vaginal delivery including: non-vertex presentation, placenta previa, prior classical cesarean, etc. • Inadequate neuraxial anesthesia: epidural or combined epidural-spinal anesthesia (subjects without adequate pain control tend to push involuntarily and cannot delay pushing) • Pregnancy complications requiring expedited delivery: severe preeclampsia, placental abruption, maternal cardiac disease, active hepatitis, HIV infection, chorioamnionitis at randomization • Fetal head visible at the introitus at complete cervical dilation • Known major fetal anomaly (defined as any significant structural abnormality that is anticipated to impact organ function e.g. cardiac defect, gastroschisis, omphalocele, hydrocephalus, facial clefts). • Intrauterine fetal death

D4. Outcome Measures

D4-1. Primary aim

Primary outcome measure: The primary outcome is spontaneous vaginal delivery, defined as delivery that occurs without the use of forceps, vacuum, or cesarean, as the primary outcome measure. This is because spontaneous vaginal delivery is the *most desirable outcome* for laboring women in the second stage of labor. Compared to cesarean delivery, spontaneous vaginal delivery is associated with *lower maternal and neonatal morbidity*, including hemorrhage, postoperative wound infection, endometritis, and prolonged hospitalization. Further, once a cesarean is performed, the risk of delivery by cesarean for future pregnancies is dramatically elevated [15], further increasing maternal morbidity. *Finally, although operative vaginal delivery is associated with overall lower maternal morbidity than cesarean delivery, it carries higher risks of neonatal and maternal pelvic floor injury than spontaneous vaginal delivery.*

Secondary outcome measures: Operative vaginal delivery (forceps or vacuum), cesarean delivery, total duration of second stage, duration of active pushing, postpartum hemorrhage, chorioamnionitis in the second stage, endometritis.

D4-2. Secondary aim#1

Outcome measure: The outcome measure for this aim will be neonatal composite morbidity, defined as occurrence of any of the morbidities in **Table 2**. In our pilot study of a consecutive prospective cohort of 5000 term births at WUMC, 100% of non-anomalous neonates admitted to the NICU had one or more of these diagnoses.

Table 2: components of composite neonatal morbidity

Morbidity	Definition
Neonatal death	Neonatal death prior to discharge
Major birth injury	Serious neonatal injury including skull fracture, brachial plexus injury, cephalohematoma
Acidemia	Umbilical cord arterial pH <7.10
Respiratory distress	Nasal flaring, subcostal and intercostal retractions, and need for supplemental oxygen to maintain oxygen saturations > 95% [22]
Transient tachypnea	Respiratory rate >60/min with or without supplementary oxygen to maintain oxygen saturation > 95%
Meconium aspiration with pulmonary hypertension	Respiratory distress and transthoracic echocardiographic findings of main pulmonary artery pressures (right-left shunting across the PDA and atria, a flattened septum, and a tricuspid regurgitation jet) [23]
Hypoxic-ischemic encephalopathy	One or more of: umbilical artery arterial pH < 7.0, base deficit > -16, need for respiratory support at 10 minutes of life, 5-minute Apgar score < 5 – and – Moderate-severe neonatal encephalopathy (NICHD criteria) or seizure activity [24]
Hypoglycemia	Venous blood glucose < 40mg/dL
Suspected sepsis	Symptomatic neonate, defined as one or more of: respiratory distress, temperature instability, apnea, lethargy – <i>with or without</i> – Abnormal CBC (6-12 hours after birth, with leukopenia or leukocytosis with an I:T ratio of >0.2) and/or positive blood culture

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D4-3. Secondary aim#2

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Outcome measures

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1) Rate and extent of acute levator ani muscle (LAM) injury in nulliparous women.

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i. Overt LAM injury, defined as clinically diagnosed 2nd, 3rd, and 4th degree perineal lacerations.

423

ii. Occult LAM injury, defined as interruption in LAM on 3D transperineal ultrasound) injury

424

2) Rates and extent of signs of POP on objective clinical examination at the 4 – 8 weeks, and 5 – 7 months postpartum follow-up visits using the validated Pelvic Organ Prolapse Quantification (POP-Q) system.

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3) Rates of patient-reported symptoms of urinary incontinence (UI), fecal incontinence (FI), and pelvic organ prolapse (POP) on validated quality-of-life questionnaires at 1 – 5 days, 4 – 8 weeks, and 5 – 7 months postpartum.

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E. STUDY PROCEDURES

E1. Recruitment

We will employ familiar efficient recruitment techniques we have used in recent randomized trials in the same settings [25-27]. All women admitted to the labor and delivery units of the participating medical centers will be screened against inclusion and exclusion criteria. Eligible subjects will be approached for written consent (**Appendix 1**) to participate in the study once they are committed to a vaginal delivery attempt. Although consent to participate will be obtained irrespective of cervical dilation, randomization will be performed only when complete cervical dilation is confirmed. This is necessary to avoid situations in which subjects are randomized and subsequently undergo cesarean delivery in the first stage of labor for indications such as failure to progress or non-reassuring fetal heart tracing [28].

E2. Randomization

Enrolled subjects will be randomly assigned in a 1:1 ratio to immediate or delayed pushing. A web-based randomization sequence will be prepared using blocks of variable sizes, stratified by study site, and maintained centrally by the study statistician [29]. The advantage of this method is that it provides a good probability of balance, and future assignments are unpredictable. In addition, it allows an explicit randomization analysis to be conducted with relative ease. Stratification by center assures balance between the two treatment groups within each center to account for possible differences in patient management. A subject's group assignment will be obtained only after the subject is confirmed to continue to meet inclusion criteria, and a study number and 10-cm cervical dilation are entered and locked in a secure web site upon complete cervical dilation.

E3. Blinding

Although blinding of both subjects and physicians would be ideal, blinding is clearly not possible in this trial. We will minimize systematic bias by applying the same standard procedures for managing labor and delivery in all patients. Further, the group assignment of subjects will not be taken into account by research personnel collecting neonatal and maternal outcomes and maternal pelvic floor morbidity. Importantly, the primary outcome of spontaneous vaginal delivery is an objective measure.

E4. Interventions

Interventions to be compared in this trial are the two most common approaches to initiating maternal pushing in the second stage of labor:

1. Immediate pushing: Women in this group will be instructed to initiate pushing as soon as complete cervical dilation is documented. Maternal position, technique (closed or opened glottis), and duration and frequency of maternal pushing effort will be at the discretion of each subject's nurse or physician.

2. Delayed pushing: Women assigned to the delayed pushing group will be instructed to wait for 60 minutes from complete cervical dilation before pushing. Women will be allowed to push earlier if they feel an irresistible urge to push or there is a clinical indication to initiate pushing. We chose 60 minutes as the delay time because our meta-analysis suggested that the duration of delay (ranging from 60 to 180 minutes) did not modify the effect of delayed pushing on spontaneous vaginal delivery rates [30]. Additionally, a 60-minute delay will enable us to assess the effect of delayed pushing without unduly increasing total duration of the second stage. This is important because, although there is no established threshold, a number of large cohort studies suggest incremental increase in the risks of operative delivery, maternal infection, hemorrhage, and laceration, as well as neonatal Apgar score depression, worsening cord pH, and neonatal morbidity, with each additional hour in the second stage, regardless of whether patients pushed immediately or delayed pushing [2, 4, 6, 7]. Finally, patients indicated in our survey that they would prefer to wait no longer than 60 minutes after complete cervical dilation before pushing if they were randomized to the delayed pushing group.

E5. Pelvic Floor Assessment

The pelvic floor assessment will be performed at all sites. These assessments will be overseen by Co-I **Dr. Richter**, a Urogynecologist and site the UAB PI of the NIH-funded Pelvic Floor Disorders Research Network. Patients willing to participate in the pelvic floor assessment part of the study will be consented (**Appendix 2**).

E5-1. Postpartum three-dimensional transperineal ultrasound imaging

Traditionally, MRI has been used to detect LAM injury, but investigators have recently validated the use of 3D ultrasound to assess acute LAM injury [10]. We will use ultrasound because it is a much more readily available and inexpensive tool than MRI. Subjects enrolled at WUMC, UAB, OHSU and PENN will be asked to consent for pelvic floor assessment including postpartum 3D transperineal ultrasound examination. Examinations will follow methods developed and validated by Dietz and Simpson [31] (**Fig. 2**). Briefly, the GE Voluson System (GE Medical System Kretztechnik GmbH & Co OHG, Zipf, Austria) with a RAB 4-8- RS 4–8 MHz Realtime 4D convex transducer will be



Figure 2: Transducer placement for transperineal ultrasound

used for the examinations. The probe will be positioned longitudinally, parting the vulvar labia in the area of the fourchette and perineal body, with minimal pressure being applied. The transducer axis will be oriented in the mid-sagittal plane to visualize the symphysis pubis from right to left. To assess levator ani integrity, we will use a surface rendering and tomographic multislice imaging technique with 2.5-mm slice intervals, from 5 mm below to 12.5 mm above the plane of minimal hiatal dimensions. Occult injury to the LAM will be documented as a discontinuity in the normal echotexture of the LAM, evident as a hypoechoic or anechoic lesion interrupting the normally hyperechogenic course of the muscle (**Fig. 3**).

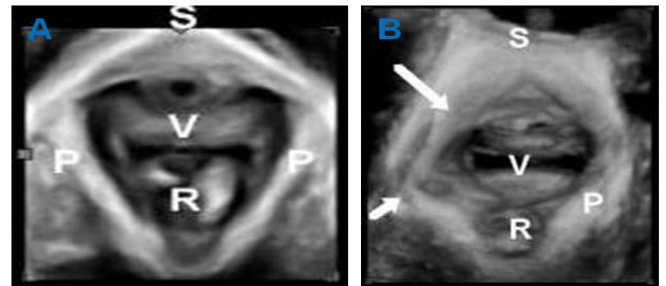


Figure 3: Surface rendered axial plane view of the perineum. Panel A shows evenly hyperechoic normal levator ani muscle. Panel B shows hypoechoic discontinuity in the muscle (arrows), representing levator ani injury. P, puborectalis muscle; R, rectum; S, symphysis pubis; V, vagina.

All image acquisitions will be performed by an experienced sonographer, highly trained in pelvic 3D ultrasound, at each site. The sonographers will undergo study-specific training and certification. **Dr. Mark Lockhart**, a radiologist with extensive experience in pelvic floor imaging, will provide oversight for pelvic sonography at UAB, while Dr Tom Gregory (Urogynecologist at OHSU) will provide oversight at OHSU. **Dr. S Abbas Shobeiri**, who has extensive experience in 3D transperineal ultrasound, will train personnel and supervise image acquisition at all sites. Dr. Shobeiri will also undertake all image processing and interpretation. Drs. Shobeiri and Lockhart, as well as other trained personnel, will be blinded to the group assignments of the subjects.

Imaging will be performed at 1-5 days, 4-8 weeks and 5-7 months postpartum.

E5-2. Assessment of pelvic floor morbidity

We will conduct a comprehensive assessment of the pelvic floor to include all components outlined in the proceedings of the NIH Terminology Workshop for Research in Pelvic Floor Disorders [32]. These assessments will be overseen by Co-I **Dr. Richter**, a Urogynecologist and site PI of the NIH-funded Pelvic Floor Disorders Research Network with extensive experience in the use of these instruments for pelvic floor research.

1) POP-Q staging of pelvic organ prolapse (4 – 8 weeks, and 5 – 7 months postpartum): Objective assessment of pelvic organ prolapse will be based on the POP-Q system, an objective, site-specific system for describing, quantifying, and staging pelvic support in women [33] (**Appendix 3**). We will follow standard guidelines established by the International Continence Society. Pelvic examinations will be performed in the dorsal lithotomy position with the subject straining maximally.

2) Symptom and Quality-of-Life Questionnaires (1-5 days, 4 – 8 weeks, and 5 – 7 months postpartum): We will use four validated Symptom and Quality-of-Life Questionnaires to assess subjective symptoms of pelvic floor morbidity (**Table 3**). Detailed description and samples instruments are located in **Appendix 4** (“QOL Evaluative Instruments”).

Table 3: Symptom and Quality of Life Questionnaires for assessment of pelvic floor morbidity

Instrument (target group)	Description
Fecal Incontinence Severity Index (FISI) ^[34] . (Women with any degree of fecal incontinence.)	<ul style="list-style-type: none"> • Applies a type and frequency matrix to obtain patient's perception of severity of four symptoms of fecal incontinence: incontinence of gas, mucus, liquid stool, and solid stool. • Patients are asked to indicate the frequency of symptoms experienced using the following scale: 2 or more times a day, once a day, 2 or more times a week, once a week, 1 to 3 times per month, or never. • Responses are weighed on a 1 to 20-severity scale and a total FISI score calculated. • Physician and patient ranking are highly correlated ($r = .97$). • <i>Fecal incontinence will be defined as at least monthly involuntary leakage of mucus, liquid stool or solid stool on the FISI.</i>
Modified Manchester Questionnaire [35] (Women with fecal urgency or any fecal or flatal incontinence on the FISI)	<ul style="list-style-type: none"> • 31-item condition-specific quality of life scale modified and validated by the Pelvic Floor Disorders Network to use American rather than British women [35]. • Highly correlated with Fecal Incontinence Quality-of-Life subscales with good test-retest and inter-rater reliability. • <i>Will be considered positive if the subject gives a response of sometimes, often, or always.</i>
Pelvic Floor Distress Inventory-20 ^[36] (assesses symptom distress) Pelvic Floor Impact Questionnaire-7 (PFIQ-7) ^[36] (assesses symptom impact)	<ul style="list-style-type: none"> • Validated short form of the Incontinence Impact Questionnaire-7 (IIQ-7); assesses UI and FI • Highly correlated with the Incontinence Impact Questionnaire long form ($r=.96$, $p<.0001$), the Colorectal-Anal Impact Questionnaire scale ($r=.96$, $p<.0001$) and the Pelvic Organ Prolapse Impact questionnaire ($r=.94$, $p<.0001$).

F. DATA MANAGEMENT

F1. Data Collection

We will collect extensive antepartum, intrapartum, and postpartum information from participants and their infants. These include, but not limited to, those listed in **Table 4**. Relevant data will be collected initially to assess eligibility. Complete baseline information will be collected if the subject is randomized. Labor course and outcome data of randomized subjects will be collected by study staff through direct interview and chart review. Data will be collected on standardized forms on which nearly all responses will be precoded (**Appendix 6-Eligibility Form, Appendix 7-Complete Data Form**).

Table 4: Outline of data to be collected

Antepartum Data (definition)	
<ul style="list-style-type: none"> • Demographic characteristics, including age and race/ethnicity • Obstetric history: gestational age (based on the estimated date of delivery as determined by the last menstrual period and confirmed by ultrasound; margin of error of ultrasound will be considered as ± 5 to 7 days by CRL up to 13 6/7, ± 7 to 10 days by fetal biometry at 14 – 22 weeks and ± 21 to 30 days by fetal biometry after 28 weeks), pregnancy complications: gestational diabetes, preeclampsia, fetal growth restriction. • Medical history: pre-existing diabetes, chronic hypertension • Maternal morphometry: maternal BMI (calculated from maternal height and weight at delivery) 	
Intrapartum Data (definition)	Postpartum and Neonatal Data (definition)
<ul style="list-style-type: none"> • Labor type (spontaneous, induced, augmented) • Estimated fetal weight by ultrasound (grams) or clinical assessment (Leopold's maneuver) • Duration of the first stage of labor (time, minutes) • Obstetric interventions (amniotomy, use of oxytocin) • Regional anesthesia data (time of initiation, type, medications used) • Fetal heart rate monitoring data (NICHD Category system assignment) • Contraction patterns • Monitoring types for EFM and contractions (internal vs external and timing of placement) • Labor complications, including nonreassuring fetal tracing and labor dystocia (diagnosed clinically) • Infectious complications, including maternal fever (oral temperature ≥ 38.0 C on one or more occasions), chorioamnionitis (diagnosed clinically and treated with antibiotics) • Fetal station and position at complete cervical dilation • Delivery information <ul style="list-style-type: none"> ○ Mode of delivery (spontaneous, vacuum or forceps assisted vaginal, cesarean) ○ Indication(s) for operative deliveries ○ Duration of second stage (minutes) ○ Duration of active pushing (minutes) ○ Postpartum hemorrhage (estimated blood loss >500ml or >1000ml following vaginal delivery or cesarean, respectively) • Maternal pelvic floor assessment information <ul style="list-style-type: none"> ○ Overt perineal lacerations (second, third and fourth degree lacerations) 	<ul style="list-style-type: none"> • Neonatal information <ul style="list-style-type: none"> ○ Birth weight (grams) ○ APGAR scores (at 1 and 5 minutes, assigned by the delivery attendants) ○ Umbilical artery pH and base excess ○ Morbidities, including respiratory distress, transient tachypnea, meconium aspiration, hypoxic-ischemic encephalopathy, hypoglycemia, suspected/confirmed sepsis ○ Nursery Disposition • Maternal infection <ul style="list-style-type: none"> ○ Maternal fever (oral temperature ≥ 38.0 C on one or more occasions during postpartum stay) ○ Endometritis (defined by the treating physicians) • Maternal pelvic floor assessment information <ul style="list-style-type: none"> ○ Levator ani injury (by 3D transperineal ultrasound) ○ Quality of life questionnaire data ○ Pelvic floor classification with POPQ

F2. Data Entry

Inclusion criteria and randomization data from participating sites will be entered in real time, screening information entered weekly, data extraction every other week, and chart completion monthly.

F3. Data Management

The study statistician (Dr. Liu) and the data manager (Ms Adelman) at WUSM will be responsible for coordinating the overall data management.

PIs at each site will be responsible for day-to-day supervision of data management, with everyone working with a common record layout. Data management at each site includes: finalizing data collection forms; procedures for data transmittal; procedures for data entry; data editing and compilation; and procedures for quality control, data verification, confidentiality, and data security.

608 Data will be collected and managed with *REDCap* (Research Electronic Data Capture), an established, secure,
609 web-based data capture and management tool developed at Vanderbilt University and supported by the
610 Division of Biostatistics at WUSM (<http://www.biostat.wustl.edu/redcap/>). The database is backed up
611 periodically throughout each day and is backed up offsite nightly.

612 Data management at the coordinating center will include monitoring of data quality and protocol adherence.

613 The study statistician and data manager will provide the following reports to the Steering Committee for
614 performance monitoring:

615 *Data quality reports:* Data quality reports will be generated monthly and include volume of missing data,
616 edits, time to edit resolution and number of overdue forms. Remedial measures, including re-
617 abstraction of data and retraining of staff, will be used as needed to minimize missing data.

618 *Performance reports:* Monthly recruitment reports to include enrollment efforts screening numbers,
619 reasons for ineligibility, and recruitment numbers. Quarterly reports performance reports will coincide
620 with Steering Committee meetings. These will be more extensive than recruitment reports and include
621 recruitment data, protocol adherence data, follow up data, and data quality assessment. Data cleaning
622 will be performed prior to quarterly reports.

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G. STATISTICAL CONSIDERATIONS

G1. Sample size and Power

G1-1. Total sample size for the trial: The sample size for the trial is estimated based on the primary outcome (Table 5). We then estimate, on the basis of the sample size for the primary aim, the power we will have to detect clinically significant differences in the secondary outcomes.

All sample size and power estimates are based on two-tailed tests. *This is important because we will be powered to detect both increases and decreases in outcomes with immediate compared to delayed pushing.* The baseline spontaneous vaginal delivery rate with delayed pushing used for the sample size estimation is based on our observational cohort [37]. We estimate that a total of **3184** (1592 delayed and 1592 immediate pushing) will be sufficient to detect a **5% absolute difference** (estimated 72% versus 77%) in spontaneous vaginal delivery with 90% power (alpha of 0.05).

Table 5: Sample size estimation for primary outcome

Detectable absolute difference	Anticipated with immediate pushing	Sample size for 90% power
10%	82%	734
9%	81%	924
8%	80%	1188
7%	79%	1578
6%	78%	2180
5%	77%	3184
4%	76%	5044

Justification: At first glance, the anticipated 5% or greater absolute increase in the spontaneous vaginal delivery rate is modest and may be seen as inconsequential. On the contrary, this translates to a combined decrease in cesarean and operative vaginal delivery rates of at least 5%. Moreover, because the potential public health impact is large, this effect size is in fact highly noteworthy. It is estimated that 40% of the 3 million women who undergo labor and delivery each year in the U.S. are nulliparous. Therefore, a 5% increase in spontaneous vaginal delivery translates to 60,000 more spontaneous vaginal deliveries and 60,000 fewer operative deliveries (12,000 second-stage cesarean plus 48,000 operative vaginal deliveries) each year. Avoiding 60,000 operative deliveries each year will have a substantial impact on overall morbidity and healthcare resource utilization in the U.S. and beyond. Because the second stage must, by definition occur to accomplish vaginal delivery, optimal management to decrease morbidities would apply to most nulliparous women delivering in developed countries, further expanding the potential impact of our findings.

G1-2. Estimated power for secondary aim #1: The sample size of 3184 for the primary outcome will be sufficient to detect a **2% absolute difference** in neonatal composite morbidity between the two groups with >80% power and significance level of 5%. This represents the difference between a 6% neonatal composite morbidity rate with delayed (based on our observational cohort study) and 4% with immediate pushing.

G1-3. Estimated power for secondary aim #2: We anticipate that at least 630 (50%) of the subjects will consent for and complete the pelvic floor aspects of the study. This will provide adequate power for the key outcomes under secondary aim #2. The rate of POP (defined as any POP at or below the hymen) or FI (based on FISl) in nulliparous women at 6 – 12 months postpartum from prior studies were 20.2% [38] and 12.6%[38, 39], respectively. Using these as baselines, the 630 women will provide >80% power to detect a 40% difference in rates pelvic organ prolapse or fecal incontinence between the two groups. For LAM injury on postpartum 3D transperineal ultrasound examination, a prior study found an average rate of 38% [40]. Using this baseline rate, 630 women will provide >90% power to detect at least a 30% difference in occult LAM injury. For overt anal sphincter injury, the sample size will be sufficient to detect a 40% difference in 2nd, 3rd, or 4th perineal lacerations (anticipated 27% to 16.2% with >80% power).

G2. Interim Analyses

We anticipate two interim analyses after 50% and 75% of the sample size are recruited, but the exact timing will be at the discretion of the DSMB. Analyses will be performed by the study statistician and presented to the DSMB, which will make recommendations regarding further conduct of the trial. At their first meeting, the DSMB will establish thresholds and rules for trial stoppage based on safety and efficacy limits. Although early stopping decisions cannot be based purely on a mathematical stopping rule, the Haybittle-Peto stopping rule will be used as a guide [41, 42]. Under this rule, the interim analyses of the primary outcome would have to demonstrate an extreme difference between groups ($p < 0.001$) to justify premature disclosure. *This rule has the advantages that the exact number and timing of interim analyses need not be specified in advance and the overall type I error is preserved at 0.05. Therefore, samples size adjustments are not needed.*

G3. Data Analysis Plan

G3-1. Overview

Data analyses will adhere closely to the CONSORT guidelines [20]. Analyses will follow the intention-to-treat principle in which subjects will be analyzed in the group to which they were randomized, regardless of whether or not they received the assigned intervention.

G3-2. Primary Analysis

Descriptive statistics will characterize the group of individuals recruited and investigate comparability of the two groups at baseline. Formal statistical testing will be limited to selected baseline characteristics considered to be prognostic factors for the primary outcome [43, 44], such as fetal station at complete cervical dilation, birth weight, and duration of the first stage of labor. The categorical prognostic factors will be compared between trial groups by using the Chi-squared or Fisher's exact tests as appropriate. Distributions of continuous prognostic factors will be assessed by visual inspection of histograms and the Kolmogorov-Smirnov test. The two-group independent t-test will be used to compare normally distributed variables. If variables are not normally distributed, the Mann-Whitney U test will be used to make comparisons between the trial groups.

The primary outcome (spontaneous vaginal delivery) and other categorical secondary outcomes will be compared between trial groups by using the Cochran–Mantel-Haenszel test. The estimates of the common relative risk and confidence intervals associated with the primary and secondary outcomes will be calculated. The Breslow-Day test for homogeneity of the odds ratios within subgroups will be reported as well. Distributions of continuous secondary outcome measures such as duration of the second stage of labor within each site will be assessed by visual inspection of histograms and the Kolmogorov-Smirnov test.

G3-3. Secondary Analyses

We will perform other analyses as needed aimed at obtaining adjusted assessments of treatment effectiveness, adjusting for baseline patient characteristics (covariates). The objectives of these analyses are to estimate the influence of covariates on the outcome and to use covariates to improve the estimated difference between treatment groups [45]. The stepwise logistic regression model stratified by study site will be used to identify and estimate the effect of multiple prognostic factors on the probability of spontaneous vaginal delivery and other categorical outcomes. For continuous secondary outcomes such as duration of the second stage, the mixed model in which study site is treated as a fixed effect will be considered to adjust for prognostic factors. Interaction tests will be used to determine whether the effectiveness of the pushing strategy significantly differs across these subgroups. These analyses will be considered exploratory in nature and will not be viewed as providing confirmatory tests of hypotheses.

The following prespecified stratified and secondary analyses will be conducted:

A. Primary Aim

The following prespecified subgroup analyses will be conducted:

1. Study site
2. Fetal station at complete cervical dilation (high versus low)
3. Fetal position at complete cervical dilation (occiput-anterior versus occiput-posterior)
4. Duration of delay prior to pushing (<30 min. versus 30 – 60 min. versus >60 min.)
5. Maternal age (<35 years versus ≥35 years)
6. Maternal Race (Black versus White versus Other)
7. Obesity (Obese versus non-obese)
8. Birthweight (<average weight versus ≥average weight)
9. Fetal sex (male versus female)

758 10. Pushing technique (spontaneous versus directed)

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760 The following planned secondary analyses will be conducted:

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1. Effect of labor onset (spontaneous versus induced) and type of induction method

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2. Effect of duration of the first stage of labor

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3. Effect of Oxytocin use in the second stage Yes versus No

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4. Effect of contraction pattern

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5. Effect of magnesium sulfate use

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6. Effect of support person in labor (Sindhu)

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7. Effect of duration of pushing

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8. Effect of chorioamnionitis (Tita)

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9. Effect of BMI (Tita)

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10. Effect of gestational age

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11. Fetal position at complete cervical dilation (Caughey)

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12. Effect of prior LEEP (Sindhu)

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13. Effect of Amnioinfusion (Sindhu)

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14. Length of hospital stay

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15. Differences in indications for cesarean and operative vaginal delivery

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16. Effect on cord blood lactate

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17. Cost-effectiveness of delayed versus immediate pushing

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18. Pelvic floor related outcomes

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i. Within and across intervention groups, correlate UI, FI and POP symptoms and impact and POPQ exams in women with/without LAM injury (control for LAM injury when comparing pelvic floor symptoms between immediate and delayed pushing groups)

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ii. Characterize rates of regression/persistence of pelvic floor symptoms/impact and objective (POP-Q and LAM) measures from 4-8 weeks to 5-7 months in the delayed versus immediate pushing groups

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iii. Characterize risk factors associated with LAM injury independent of intervention group

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iv. Characterize risk factors associate with persistence of pelvic floor symptoms

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v. Correlate overt and occult LAM injury to objective and subjective measures of pelvic floor morbidity

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vi. Rate of LAM defect on follow-up imaging after repair of overt laceration

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vii. Predictors of overt and occult LAM injury

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viii. Characterize rates of 3rd and 4th degree tears by randomized group

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ix. Characterize predictors of anal sphincter injury

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x. Predictors of anal sphincter defect following primary repair

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B. Secondary Aims (Pelvic Floor)

1. Within and across intervention groups, correlate UI, FI and POP symptoms and impact and POPQ exams in women with/without LAM injury (control for LAM injury when comparing pelvic floor symptoms between immediate and delayed pushing groups)
2. Characterize rates of regression/persistence of pelvic floor symptoms/impact and objective (POP-Q and LAM) measures from 4-8 weeks to 5-7 months in the delayed versus immediate pushing groups
3. Characterize risk factors associated with LAM injury independent of intervention group
4. Characterize risk factors associate with persistence of pelvic floor symptoms
5. Correlate overt and occult LAM injury to objective and subjective measures of pelvic floor morbidity
6. Rate of LAM defect on follow-up imaging after repair of overt laceration
7. Predictors of overt and occult LAM injury
8. Characterize rates of 3rd and 4th degree tears by randomized group
9. Characterize predictors of anal sphincter injury
10. Predictors of anal sphincter defect following primary repair

G3-4. Patient Satisfaction

We will assess patient satisfaction with their birthing experienced using the modified Mackey Childbirth Satisfaction Rating Scale (**Appendix 8**). This is a simple validated childbirth satisfaction scale which has been modified to focus on the second stage experience. Face and construct validity as well as reliability have been established [46]. Specifically, the Cronbach's alpha for the overall satisfaction score is >0.90, indicating high reliability. Respondents will indicate their degree of satisfaction or dissatisfaction with each item on a Likert scale. This modified questionnaire of 7 items will be administered within 24 hours of child birth. The primary measure will be the overall satisfaction score. We will also assess satisfaction with sub dimensions of patient satisfaction with the child birth experience. Finally, we will calculate a total satisfaction score as the sum of the scores for each individual item.

G3-5. Economic Analysis

We will conduct economic analysis to estimate medical costs associated with management of the second stage and associated outcomes quantify *potential cost savings* attributable to immediate or delayed pushing. A decision model will be developed depicting the decision of whether to use immediate or delayed pushing in the second stage of labor. For each strategy the probability of subsequently outcomes will be obtained based on results of the randomized trial. We will conduct the economic evaluation the viewpoint of health providers and purchasers; so we will only include direct costs. These costs will be those covering all aspects of intrapartum and postpartum care provided to the mother and infant between randomization and discharge from the hospital. Cost savings, if any, will be the difference between the costs in the two groups. Sensitivity analysis will be used to examine the robustness of the results.

H. PROTECTION OF SUBJECTS

H1. Assessment of Risks

H1-1. Subject Characteristics

All women undergoing labor and delivery at Washington University Medical Center and the other participating study sites during the study period will be assessed for eligibility. We anticipate enrolling a total of **3184** women over four years.

We will use broad inclusion criteria to increase generalizability of our results. In addition, because the interventions (immediate or delayed pushing) are routinely employed in obstetric practice, exclusion criteria will be limited to maternal and fetal conditions for which vaginal delivery is contraindicated or expedited delivery is required.

H1-2. Potential Risks

The potential risk to study subjects is expected to be minimal, but include the following:

1. Loss of confidential health information.
2. Although it is unclear what effect the timing of pushing will have on these outcomes, prior studies suggest increased duration of the second stage with delayed pushing.

H2. Adequacy of protection against risks

H2-1. Protection of Confidentiality

Consent from families in this minimal risk study, will be obtained in a private setting, such as a quiet conference area or the patient's private room.

Data will be collected and managed with *REDCap* (Research Electronic Data Capture), an established, secure, web-based data capture and management tool developed at Vanderbilt University and supported by the bioinformatics team at Washington University School of Medicine (<http://www.biostat.wustl.edu/redcap/>). The REDCap application executes within the private zone of the WUBIOS Computing Resource within the Division of Biostatistics. This private zone is separated from the Internet and the general WUSTL network by a firewall. WUBIOS is a professionally managed, HIPAA compliant network which has been approved by the WUSM security officer. Access to REDCap is restricted to either computers which are located within WUBIOS or other WUSM secure networks (e.g. WUCON) or which have a WUBIOS issued digital certificate installed in the user's browser. Users of REDCap are required to sign a user agreement and be authorized by their supervisor. A user specific userID/password is required for logging into REDCap. For each research project, IRB approval is required and an administrator within the project grants specific users access rights to the project. Read or Read/Edit privileges are granted on a form-by-form basis for each user. Rights to download data are also controlled by the project administrator.

As the data are entered into the electronic database, the database will be double-password protected (one level requires a password to access the network, and the second is the password to the study database). Only research staff of this project will have authorization to access the files, with permission controlled by the Data Manager; all other access will be prohibited. Access to the files will be logged electronically, and access will only be made for the purposes of conducting the study.

All data collected for this study will be used for research purposes only. The data collected from the medical record will be limited to only what is necessary to carry out the study as outlined. No data from the study will be reported on an individual basis; all findings from this study will be reported in statistical summary form only. All members of the research team will treat all data with strict confidentiality. Each subject will be assigned a unique study code number that will be used on all data forms. A list of patient names and study code numbers will be maintained separately from the data extraction forms, under secured lock. Only the investigators and project staff, with the proper training on research practices including the protection of confidentiality, will have access to this information. The data extraction forms will be kept in a double locked fashion; in a locked, temperature-protected file cabinet that only the research nurse coordinator and research nurse have access to.

H2-2. Safety monitoring

The interventions compared in this trial are immediate and delayed pushing in the second stage of labor. Both techniques are extensively used in current obstetric practice. Therefore, no serious or life-threatening adverse events are expected. Nonetheless, the following measures will be taken to monitor and investigate adverse events:

1. **Independent Data and Safety Monitoring Board (DSMB):** We have established an independent study-specific Data Safety and Monitoring Board (DSMB) to oversee the trial. Members of the DSMB are Dwight Rouse, MD, MSPH (Brown University)-chair; Mark Klebanoff, MD (Ohio State University); and Cande Ananth, PhD, MPH (Columbia University) who represent the appropriate expertise (perinatology, epidemiology, biostatistics, neonatology, and clinical trials) and will provide appropriate oversight to assure that the trial accrues at a sufficient rate, and that the safety and privacy of all study participants is assured. Members are not involved in any aspect of the trial operation. The DSMB will meet regularly to review study progress and to monitor adverse events. The DSMB will be confidentially briefed by the Data Management Center before each meeting regarding study progress (recruitments and drop-outs), and study outcomes. The DSMB will issue a written report to the investigators after each meeting outlining any study problems or needed actions.
2. **Adverse events reporting:** Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol (Table 6).

Table 6: Adverse events and serious adverse events**Table 6a: Adverse events**

Adverse Event	Definition
Acidemia	Umbilical cord arterial pH <7.1
Chorioamnionitis in the second stage of labor	Chorioamnionitis as diagnosed by the treating physician after complete dilation (after trial entry)
Severe postpartum hemorrhage	Estimated blood loss >1000ml for vaginal delivery and >2000ml for cesarean
Neonatal intensive care unit admission (NICU)	NICU admission > 12 hours for any reason prior to hospital discharge

Table 6b: Serious adverse events

Serious adverse event	Definition
Maternal	
Maternal death	Any maternal death
Life-threatening maternal event	Life threatening events in the mother are defined as those that in the view of the research staff and PI put the individual patient at imminent substantial risk of dying, or if continued participation in the study might have resulted in death
Maternal admission to the intensive care unit	Maternal admission to the intensive care unit for any indication
Unplanned hysterectomy	Unplanned hysterectomy performed during cesarean or following a vaginal delivery
Neonatal	
Neonatal death	Neonatal death prior to discharge
Life-threatening neonatal event	Any life-threatening neonatal event, defined as those that in the view of the research staff and PI put the individual patient at imminent substantial risk of dying, within the first 24 hrs. of life
Serious neonatal birth injury	Major neonatal injury including skull fracture, brachial plexus injury, cephalohematoma

The DSMB will review all Adverse Event Reports and other interim safety data and will provide a report to the Steering Committee and to the local IRBs in compliance with local standards. If a participant develops a

serious adverse event, the safety of continuing the intervention will be ascertained by the participant's obstetric care provider in collaboration with the site PI.

3. **Interim analyses:** We anticipate two interim analyses after 50% and 75% of the sample size are recruited, but the exact timing will be at the discretion of the DSMB. Analyses will be performed by the study statistician and presented to the DSMB, which will make recommendations regarding further conduct of the trial. Possible decisions include stopping the study because efficacy has been achieved or because of futility, and modifying the target sample size. At their first meeting, the DSMB will establish thresholds and rules for trial stoppage based on safety and efficacy limits. However, the Haybittle-Peto stopping rule will be used as a guide.

H3. Potential Benefits/Importance of knowledge gained

The study is not designed to provide direct benefits to research participants. Nonetheless, if our hypothesis that immediate pushing in more efficacious is correct, then subjects randomized to immediate pushing will have the benefits of increased rates of spontaneous vaginal delivery and reduced maternal and neonatal complications. More importantly, results from this study have the potential to improve outcomes for women undergoing labor and delivery. Because the anticipated risk to participants is minimal, the risks-benefit ratio is very favorable.

I. TRIAL ADMINISTRATION

I1. Leadership: Multiple Principal Investigator Plan

I2-1. Rationale

The rationale for two PI/PDs is three-fold. *First*, this multicenter clinical trial involves the recruitment of a large numbers of patients, collection of extensive data, and management of several investigators across four sites and two sub-sites. The large scale and complex nature of this trial is best accomplished if led and shared by two PIs. *Second*, Drs. Cahill and Tuuli have complementary, successful scientific backgrounds. Dr. Cahill has experience as the PI for large-scale prospective obstetric outcomes studies, as well as experience as a key co-investigator in multicenter studies. Dr. Tuuli has extensive experience in trial design and completion in the obstetric population. Both share technical expertise, formal research and epidemiologic training, and interpretative skills. This grant is strengthened by the interplay of clinical, epidemiologic, and implementation expertise provided by these PIs and their co-investigators. *Third*, both Drs. Cahill and Tuuli have worked together intensively over the past four years through frequent meetings and strong collaborative interactions as clinical colleagues and, most importantly, as scientific colleagues, completing a number of research projects within the same patient population that will be investigated in this proposal. Drs. Cahill and Tuuli have a track record of working together on clinical research, with several joint publications including those that provided the preliminary evidence for this trial. As such, the idea for this study was developed jointly by the two PIs.

I2-2. Roles

Dr. Armin Cahill is a board certified Obstetrician Gynecologist with a sub-specialty in Maternal-fetal Medicine. She has formal training in conducting clinical research as a perinatal epidemiologist with a Master's of Science in Clinical Investigation from the Washington University School of Medicine CTSA (UL1RR014992; PI Evanoff). Her neonatal and maternal outcomes research focuses on term birth outcomes and electronic fetal monitoring. Dr. Cahill has extensive experience in clinical research design, collaboration (specifically with Dr. Tuuli, as well as Drs. Macones, and the site PIs), conduct, and publication, and her clinical training supports her ability to assess antenatal and perinatal influences on neonatal phenotypes. Her roles in the project will include participant recruitment and retainment (with the lead research nurse and Ms. Anderson), data management (with Ms. Adelman), budget oversight (with Ms. Anderson), analyses (in collaboration with Dr. Liu and the biostatistical core), and manuscript drafting. **Dr. Methodius Tuuli** is a Maternal-Fetal Medicine sub-specialist and a Master of Public Health who has expertise conducting Phase III trials in the obstetric population. He is an NIH-sponsored Women's Reproductive Health Research Scholar who collaborates frequently with Drs. Cahill, Macones, and Colditz.. His research skills have informed the trial hypotheses, design, and analytic plan. Dr. Tuuli's role in this project will include trial conduct and randomization (working closely with Dr. Liu), supervision of the ultrasound evaluation of perineal injury (in conjunction with Dr. S. Abbas Shobeiri), liaising with the DSMB and the Steering Committee, informing the statistical analyses (with Dr. Liu), and manuscript drafting.

The complementary roles of Drs. Cahill and Tuuli are shown in the table below:

PI/PD	Administrative	Technical Oversight	Scientific
Dr. Alison Cahill	1. Screening, retention 2. Budget oversight 3. Clinical staff management	1. Clinical recruitment 2. Data collection and management	1. Over-all data analysis 2. Manuscript drafting
Dr. Methodius Tuuli	1. Trial conduct 2. Data safety and monitoring 3. Site liaison	1. Ultrasound data collection 2. Multi-site randomization	1. Ultrasound analysis 2. Manuscript drafting

The scientific roles are clear between the PI/PDs and amongst the site PIs and the extended collaborative team. For all primary data from the proposed study, the PI/PDs will be directly involved in manuscript drafting and submissions for presentations. *Drs. Cahill and Tuuli will have first and senior author positions, at their discretion, on primary data presentations and publications.* The conduct of any additional analyses will be done with the permission of both PI/PDs, and authorship will be decided jointly with the steering committee.

I2-3. Communication: Ongoing communication is well facilitated within the current environment. Drs. Cahill and Tuuli currently meet weekly regarding other ongoing research collaborations, including the preliminary and preparatory studies for the current proposal. Drs. Cahill and Tuuli have offices 30 feet from each other. For this proposed study, the Washington University team will meet weekly, led by the PI/PDs; the PI/PDs will meet weekly regarding governance and administration (Dr. Liu will attend once a month to review biostatistics); and the PI/PDs will meet with the site-PIs by video conference every other week. At every other of these meetings, the pelvic floor team including Director (Dr. Richter) and key collaborators (Drs. Shobeiri and Lockhart) will also join. In attendance at the Washington University site meeting will be the research nurse coordinator, research nurse, data manager (Ms. Adelman), sonographer, and research assistant. Dr. Macones will be in attendance every other week for oversight, and the data and biostatistical teams will attend as needed. These meetings will cover, but not be limited to, review of the number of patients screened and recruited, ongoing status with conduct and challenges, enrollment, and IRB and report needs. An overview of a representative month's meeting schedule is as follows:

Week	Monday	Tuesday	Wednesday	Thursday	Friday
1	PI/PD weekly meeting		Washington University trial team (with Dr. Macones)	PI/PDs and site-PIs (via video conference)	
2	PI/PD weekly meeting		Washington University trial team		
3	PI/PD weekly meeting		Washington University trial team (with Dr. Macones)	PI/PDs, site-PIs, and Pelvic floor team (via video conference)	
4	PI/PD weekly meeting (with biostatistics)		Washington University trial team		

I2-4. Decisions: Leadership decisions regarding all aspects of the study, from staffing to research direction, will be made jointly by Drs. Tuuli and Cahill. Decisions specific to areas of the study will be made together with the appropriate staff or collaborators.

I2-5. Scientific Direction: Scientific direction is well described in the trial protocol. However, if unanticipated findings were to arise, such as those from interim analyses, study direction would be discussed and decided on jointly by both PI/PDs and would be informed by the guidance of the Steering Committee, led by Dr. Colditz, as well as by the Data Safety and Monitoring Board (led by Dr. Dwight Rouse). This type of scenario is one in which the complementary experience and specialties of the PIs, as well as the extensive and broad experience

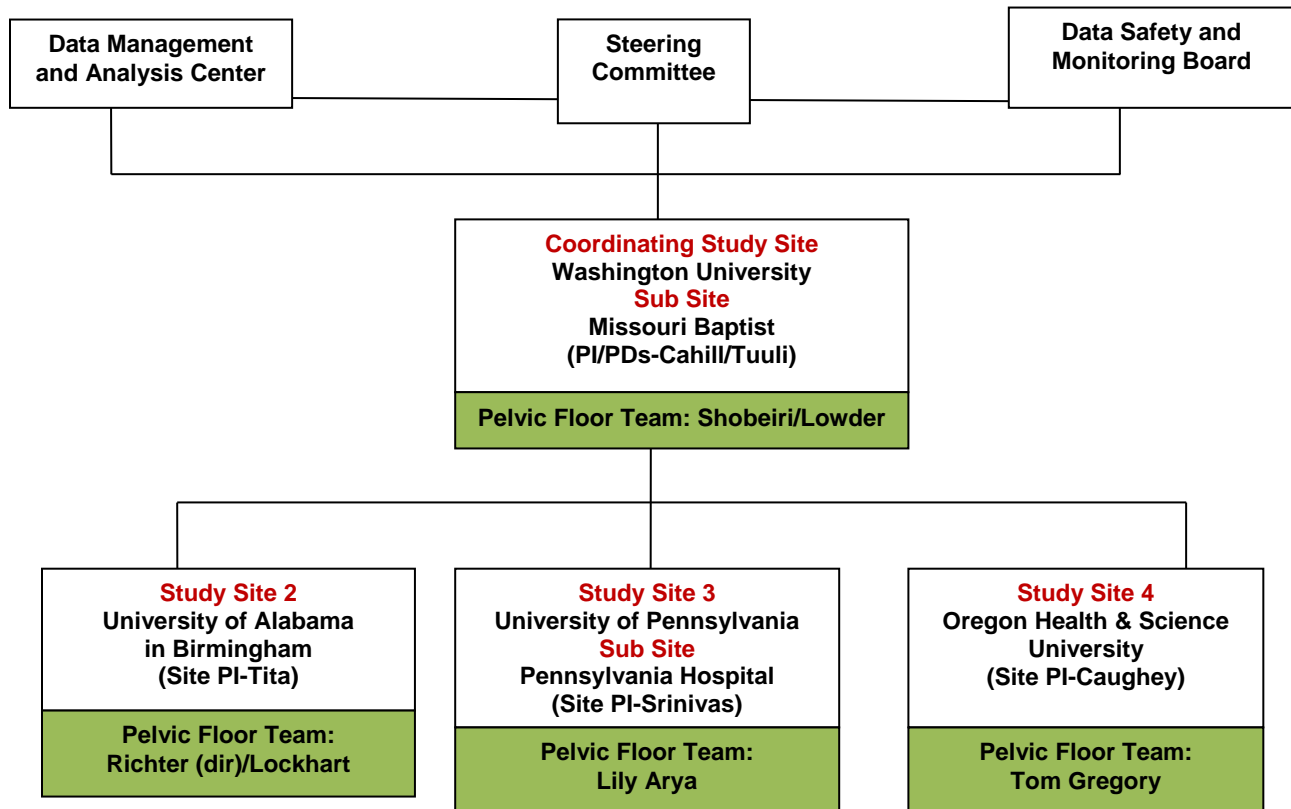
of their collaborators and leaders and members of the oversight boards, will benefit the science and help assure the success of the project. Likewise, if unexpected findings were to arise from the pelvic floor portion of the study, the same process would be followed, further informed by the expertise of Drs. Richter, Shobeiri, and Lockhart.

I2-6. Conflict Resolution: If conflict were to arise, resolution would be sought jointly between Drs. Cahill and Tuuli. Although Drs. Cahill and Tuuli have a track record of successful collaboration, and therefore the likelihood of inability to reach resolution is remote, additional steps would be pursued if necessary. Unresolved conflict would be brought to the Steering Committee, led by Dr. Colditz, which will have an uneven number of members in the event that a vote would be necessary. In addition, the Washington University School of Medicine recognizes the possibility of potential conflict in scientific endeavors and provides mechanisms for third-party arbitration and guidance; in this case, Dr. Bradley Evanoff (PI of the School's CTSA) would assist in arbitration and resolution if the occasion of unresolved conflict were to arise.

I2. Organizational Plan

As a four-site study with two sub sites, leveraging the experienced collaborating investigators, governance will be shared rather than directed by a highly centralized and hierarchal design.

I2-1. Administrative structure



- Coordinating Study Site for the trial at Washington University in St. Louis, School of Medicine
- Data Management and Analysis Center at Washington University in St. Louis, School of Medicine
- Study sites:
 1. The University of Alabama, Birmingham, AL
 - Director of the Pelvic Floor Assessment team: Dr. Richter (UAB)
 2. Oregon Health and Science University, Portland, OR
 3. University of Pennsylvania, Philadelphia, PA
 - Sub site: Pennsylvania Hospital
 4. Washington University in St. Louis, School of Medicine (WU)
 - Sub site: Missouri Baptist

I2-2-1. Coordinating Study Site, WU, will be responsible for:

- Maintaining the study protocol and making revisions
- Updating the site operations manual as needed
- Performing overall management and coordination of the trial and measurements
- Ensuring all Institutional Review Board requirements are up to date at all sites
- Over-seeing and assisting with recruitment, monitored by the data management and analysis team at WU
- Providing training and support for data collection instruments and quality assurance and control
- Coordinating progress reports to the data management center at WU

I2-2-2. The Data Management and Analysis Center, WU, will be responsible for:

- Creation of the database and extraction tools
- Data cleaning, outlier detection, and preparation for analysis
- Analyses of interim data
- Additional analyses as requested by the DSMB
- Primary intention-to-treat analyses per protocol
- *A priori* planned secondary analyses per protocol

I2-2-3. Participating Clinical Sites will be responsible for:

- Screening and recruiting participants
- Managing and operating the site
- Determining participant eligibility
- Designating group assignment as specified by central randomization
- Data entry
- Developing site-internal procedures and training/certifying staff members as appropriate
- Assuring compliance with Institutional Review Board requirements
- Responding to Quality Assurance visit reports
- Maintaining good recruiting rate
- Reviewing and reconciling study data
- Entering participant data into study database and responding to data cleaning requests
- Submitting inquiries on procedural issues to the Coordinating Center
- Responding to all requests for data regarding interim and final analyses and data safety

I2-3. Data Safety and Monitoring Board (DSMB)

A DSMB has been established to ensure objective oversight of the trial's safety and conduct. The members of the DSMB are:

- Dwight Rouse, MD (Brown University)-**Chair**
- Mark Klebanoff, MD (Ohio State University)
- Cande Ananth, PhD, MPH (Columbia University)

This group has complementary expertise in clinical trials, maternal-child health, obstetric and pediatric outcomes-based research, and epidemiology. Members are not involved in any aspect of the trial operation. The DSMB will meet regularly to review study progress and monitor adverse events. The DSMB will be confidentially briefed by the data analysis center before each meeting regarding study progress (recruitment and drop-out rates), and study outcomes. None of that information will be available to the study investigators unless disclosed by the DSMB. The DSMB will issue a written report to the investigators after each meeting outlining any study problems or needed actions.

I2-4. Steering Committee

148 The SC will comprise:

- 149 • Dr. Graham Colditz-**Chair** (brings extensive experience and expertise in coordinating large multicenter
- 150 studies)
- 151 • NICHD Representative (Dr Uma Reddy)
- 152 • The PI/PDs (Drs. Cahill and Tuuli)
- 153 • The site-PIs (Drs. Caughey, Tita, and Srinivas)
- 154 • Director of the pelvic floor team (Dr. Richter)

155 Each member is a voting member and the chair may vote to break a tie.

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157 The functions and responsibilities of the SC are:

- 158 • Decision making regarding participant eligibility and study end points
 - 159 • Publication and presentation guidelines
 - 160 • Authorship determination
 - 161 • Consideration and approval for ancillary studies
 - 162 • As needed addressing of scientific or operational matters as they arise
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J. STUDY TIMELINE

J1. Timeline of Study Activities and Milestones

Project Period	0-6 months	6-12 months	12-18 months	18 -24 months	24-30 months	36-42 months	42-48 months	48-54 months	54-60 months
ACTIVITIES									
Protocol Development									
Trial registration									
Staff recruitment and training									
Study forms and database									
Subject recruitment/trial									
Subject recruitment/pelvic floor									
Data collection & management									
Data analysis									
Drafting of manuscript & reports									
MILESTONES									
Protocol & IRB finalized	x								
Recruitment start		x							
50% recruitment					x				
75% recruitment							x		
Interim analysis					x		x		
100% recruitment								x	
Pelvic floor follow up complete								x	
Data analysis complete									x

J2. Training

Prior to start of the trial, training of research personnel on the manual of operations will take place. Each center will be required to certify that personnel are familiar with eligibility criteria, study procedures, and data collection and management.

J3. Final Analysis

Data collection for the trial will be expected to be completed 8 months after the last subject is enrolled. After a two-month period for compilation of data entry and cleaning, the data set will be locked and available for final analysis.

J4. Publication Policy

Detail publication and author guidelines will be determine by the steering committee. However publication of results by individual centers without prior approval of the Steering Committee is unacceptable.

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