

# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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This supplement contains the following items:

1. Original protocol
2. Final protocol
3. Summary of changes

Please note that the statistical analysis plan is contained within the study protocol.

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# Induction in Nulliparous Women at 39 Weeks to Prevent Adverse Outcomes: A Randomized Controlled Trial

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## Protocol

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### A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

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# **1 Introduction**

## **1.1 Study Abstract**

Recently, several retrospective studies have shown that certain maternal and perinatal complications increase with gestational age after 37-38 completed weeks. This has called into question whether it is appropriate to wait until 41 weeks for induction in uncomplicated pregnancies. Although it has traditionally been held that the disadvantage of labor induction is that it increases the risk of cesarean delivery, this conclusion is based on studies with methodological flaws. In these studies, women who were electively induced were compared by gestational week with those who labored spontaneously. This is not the most appropriate comparison group because women who are induced at 39 weeks, for example, would not otherwise have immediate spontaneous labor. Instead, the most fitting comparison group should be composed of women who are expectantly managed. The studies that have used this comparison group have largely failed to demonstrate the association between induction and cesarean delivery, as have the small trials where women were randomized to labor induction or expectant management. Thus, whether labor induction at 39 weeks of gestation modifies maternal and perinatal outcomes, compared with expectant management, remains unknown.

This protocol describes a randomized trial of 6000 women to assess whether a policy of elective induction of labor at 39 weeks of gestation compared with expectant management will improve outcomes.

## **1.2 Primary Hypothesis**

Among nulliparous women with singleton uncomplicated term pregnancies, elective induction of labor at 39 weeks, compared with expectant management, reduces the risk of severe neonatal morbidity and perinatal mortality.

## **1.3 Purpose of the Study Protocol**

This protocol describes the background, design and organization of the randomized clinical trial and may be viewed as a written agreement among the study investigators. The Data and Safety Monitoring Committee (DSMC) and the Network Advisory Board review the protocol. Before recruitment begins, the protocol is approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network Steering Committee, and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs; major changes also require the approval of the DSMC.

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

## 2 Background

### 2.1 Introduction

Post dates pregnancy, defined as a gestation that persists beyond 294 days or 42 weeks' gestation, is associated with an increased risk of perinatal morbidity and mortality.<sup>1</sup> Several studies have shown that as pregnancy extends beyond 42 weeks the risk of oligohydramnios, macrosomia, fetal birth injury, meconium aspiration syndrome, and stillbirth increase significantly.<sup>1</sup> To avoid these risks, common practice has been to induce labor once 42 weeks has been reached. Indeed, because these risks begin to increase even before 42 weeks, many investigators have suggested that a policy of induction of labor at 41 weeks can improve pregnancy outcomes. In 2006 a Cochrane review was conducted of all trials in which women were randomized to induction of labor at 41-42 weeks or expectant management with fetal surveillance (including the MFMU Network's trial). The investigators found that a policy of induction of labor at or beyond 41 completed weeks was associated with fewer (all-cause) perinatal deaths (RR 0.3 95% CI 0.09, 0.99), with no evidence of a statistically significant difference in the cesarean section rate for women in the induction group (RR 0.92 95% CI 0.76, 1.12).<sup>2</sup>

The American Congress of Obstetricians and Gynecologists states that both expectant management and labor induction at 41 weeks are associated with low complication rates and good perinatal outcomes in low-risk post term women but that there appears to be a small advantage to labor induction, regardless of parity or method of induction.<sup>1</sup> Recently, data have been published showing increased rates of complications beyond 39 weeks, suggesting that it may be advantageous to induce uncomplicated pregnancies at an earlier gestation than 41 weeks.<sup>3-15</sup>

### 2.2 Complications of Term Pregnancies beyond 39 Weeks of Gestation

#### 2.2.1 Maternal Complications

Several studies have demonstrated that certain maternal complications increase in a continuous fashion after 37-38 completed weeks.<sup>3-8</sup> Investigators have reported that pregnancies that continue beyond 39 weeks are associated with increased risks of cesarean section, operative vaginal delivery, 3<sup>rd</sup> and 4<sup>th</sup> degree lacerations, and chorioamnionitis.<sup>3-7,9</sup>

Table 1 summarizes the maternal data from the largest and most recent cohort studies that have examined adverse outcomes in term pregnancies. Most of these studies examined maternal complications in multivariable models and found that gestational age beyond 39 weeks was predictive of increased risk even when controlling for known confounders such as maternal age, ethnicity, education, parity, length of labor, induction, and birth weight.

Table 1. Maternal Complications in Singleton Gestation by Gestational Week

Population and Reference	39 weeks	40 weeks	41 weeks	Adjusted OR (95% CI) 41 wks vs 39 wks in a Multivariable Model
<b>Primary cesarean delivery (multiparas and nulliparas)</b>				
N=45,673; 1992-2002 <sup>4</sup>	14.0%	15.9%**	21.2%**	1.32 (1.17, 1.53)
N=32,828; low risk; 1976-2001 <sup>3</sup>	9.2%	10.4%**	14.1%**	1.44 (1.28, 1.62)
N=119,254; low risk; 1995-99 <sup>5</sup>	8.8%	9.0%	14.0%**	1.28 (1.20, 1.36)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	12.8%	14.1%**	19.8%**	1.46 (1.44, 1.48)
<b>Primary cesarean delivery rates by weeks' gestation in nulliparas only</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	11.4%	14.2%*	18.9%**	Not available
N=119,254; low risk; 1995-99 <sup>5</sup>	14.4%	14.9%	21.9%**	Not available
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	21.5%	23.3%**	30.1%**	Not available
<b>Operative vaginal delivery</b>				
N=45,673; 1992-2002 <sup>4</sup>	15.5%	17.9%**	18.5%	1.14 (1.05, 1.23)
N=32,828; low risk; 1976-2001 <sup>3</sup>	14.8%	16.4%**	17.4%**	1.22 (1.10, 1.44)
N=119,254; low risk; 1995-99 <sup>5</sup>	9.4%	10.9%**	13.3%**	1.29 (1.20, 1.36)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	7.6%	8.1%**	9.6%**	1.14 (1.11, 1.16)
<b>3<sup>rd</sup> and 4<sup>th</sup> degree lacerations</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	9.4%	10.8%**	12.0%**	1.26 (1.10, 1.44)
N=119,254; low risk; 1995-99 <sup>5</sup>	4.0%	4.6%*	6.7%**	1.58 (1.44, 1.73)
<b>Postpartum hemorrhage</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	13.4%	12.8%	16.0%**	1.18 (1.06, 2.31)
N=119,254; low risk; 1995-99 <sup>5</sup>	2.5%	3.1%**	4.1%**	1.21 (1.10, 1.32)
<b>Febrile morbidity</b>				
N=45,673; 1992-2002 <sup>4</sup>	1.7%	2.3%	2.7%**	1.46 (1.14, 1.87)
N=32,828; low risk; 1976-2001 <sup>3</sup>	5.2%	6.0%**	7.7%**	1.28 (1.11, 1.49)
N=119,254; low risk; 1995-99 <sup>5</sup>	2.7%	3.7%**	5.1%**	1.46 (1.14, 1.87)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	1.6%	2.0%**	2.7%**	1.49 (1.45, 1.54)

Statistical significance compared with rate of outcome in the previous week gestation: \* p<.01, \*\* p<.001



## 2.2.2 Infant Outcomes

Studies have also demonstrated that the rates of adverse neonatal outcomes are increased in pregnancies that extend beyond 39 weeks.<sup>4,6</sup> In a study of singleton deliveries in Scotland between 1985 and 1996, Smith showed that the risk of perinatal death (stillbirth or neonatal death) nadirs at 39 weeks.<sup>8</sup> In a study of deliveries registered in an area of London, the rate of stillbirth increased progressively with advancing gestation from 37 to 43 weeks.<sup>10</sup> Abnormal neonatal acid-base status has been shown to increase in pregnancies delivered beyond 39 weeks.<sup>6,11</sup>

In a retrospective cohort study of singleton, cephalic, low-risk neonates delivered at term, Caughey et al. concluded that neonatal complications of term pregnancy increase in a continuous, rather than in a threshold fashion. In this cohort the incidence of severe neonatal complications was increased 1.5-2 fold in pregnancies delivered at 40-41 weeks compared with those delivered at 39 weeks (Table 2).<sup>6</sup> Other investigators reported similar trends in neonatal morbidity for pregnancies advancing beyond 39 weeks.<sup>7,11,12</sup>

**Table 2. Association of Gestational Age with Severe Neonatal Complications**

Gestational week	Percent with complications	Odds ratio (95% CI)
39 weeks	1.84%	referent
40 weeks	2.31%	1.47 (1.09, 1.98)
41 weeks	3.14%	2.04 (1.50, 2.78)
42 weeks	3.82%	2.37 (1.63, 3.49)

Based on Caughey et al 2005; severe neonatal complications defined as birth trauma, seizures, intracranial hemorrhage, sepsis, meconium aspiration syndrome, respiratory distress syndrome

In contrast with maternal outcomes, there is clear evidence that adverse neonatal outcomes are more common when elective delivery is undertaken at term but prior to 39 weeks. Several investigations demonstrated an increase in neonatal morbidity for infants delivered at 37-38 weeks, compared with those delivered at 39 weeks or beyond. Specifically, at ages before 39 weeks, the risk of NICU admission, RDS, mechanical ventilation, and hypoglycemia are increased, particularly for infants delivered by cesarean section.<sup>13-15</sup> While the risk of both stillbirth and infant death per 1000 ongoing pregnancies increases a modest amount between 37-39 weeks (0.7/1000 to 1.4/1000 respectively), the risk of more common adverse events (e.g., RDS, mechanical ventilation) is increased by a factor of 2 to 12.<sup>14,15</sup> Overall, elective delivery prior to 39 weeks is associated with an increase in respiratory and other adverse neonatal outcomes.

## 2.3 Results from MFMU Network Studies

Secondary analyses of NICHD MFMU Network data are consistent with the findings above for both maternal and neonatal outcomes. In the MFMU Network trial of fetal pulse oximetry (FOX), a secondary analysis of 4086 women found that the risks of a composite maternal outcome (treated uterine atony, blood transfusion, or peripartum infection) and cesarean delivery increased with increasing gestational age from 39 to 41 or more completed weeks (p value for trend < 0.001).<sup>16</sup>

In the Cesarean Registry, a composite outcome of death or adverse neonatal outcome increased from 8% to 11.3% as gestational age increased from 39 to 41 weeks in women undergoing elective repeat cesarean delivery.<sup>14</sup> Also, in the cohort of women in the FOX trial referenced above, risks of a similar composite adverse neonatal outcome increased with increasing gestational age after 39 weeks.<sup>16</sup>

In summary, available data lead to the hypothesis that planned delivery at 39 weeks will result in the fewest adverse maternal and perinatal outcomes.

## **2.4 Potential Risks and Benefits of Planned Elective Induction of Labor before 41 weeks**

If neonatal risks nadir at approximately 39 weeks, and if the risks of maternal and neonatal complications increase monotonically after 39 weeks, the question arises - do the risks of pregnancy prolongation beyond 39 weeks outweigh the risks of labor induction? Whereas planned cesarean delivery in the absence of medical or obstetric complications is performed at 39 completed weeks, planned induction of labor at 39 weeks has been discouraged due to a potential increase in risk of cesarean delivery. Indeed, several retrospective cohort studies indicate that induction of labor prior to 41 weeks is associated with an approximately 2-fold higher risk of cesarean in nulliparous women.<sup>17-22</sup> However, these studies have several important limitations.

First, a number of studies compared outcomes in women undergoing both indicated and elective inductions with those of spontaneously laboring women.<sup>20,23-26</sup> By including women with medical indications for induction (e.g., preeclampsia), it is possible that the higher rates of cesarean delivery observed in the induction group were due to the pregnancy complications and not the induction per se. Other studies have evaluated elective induction of labor separately.<sup>17,18,21,22,24,27,28</sup> They consistently showed that cesarean delivery is more common in those electively induced. However, in these studies, women who were electively induced were compared with those who were spontaneously laboring. While this is a convenient comparison group it is not the most appropriate one, because women who are induced at 39 weeks are not guaranteed the alternative of an immediate spontaneous labor. In other words, women and their providers cannot choose between elective induction and spontaneous labor, but between elective induction and expectant management. Expectant management at 39 weeks may result in a proximate spontaneous labor but also may result in circumstances (e.g., preeclampsia, need for labor induction at 42 weeks) that increase the risk of cesarean.<sup>29</sup> Therefore, the most fitting comparison group in an observational study of elective induction would be all women at 39 weeks with ongoing pregnancies.

One group of investigators performed an observational study with just such a nulliparous study population. Osmundson and colleagues compared outcomes of labor between nulliparous women who either underwent elective induction or expectant management at or beyond 39 weeks at a single center.<sup>30,31</sup> Moreover, these investigators ascertained cervical status of all women at 38-39 weeks, in order to remove the possibility of selection bias related to this factor. The findings of this study, in contrast with the prior studies that used spontaneously laboring comparison groups, revealed that elective induction at 39 weeks or greater, for either women with a favorable or unfavorable cervix, did not increase the cesarean delivery rate. Specifically, for nulliparas with a favorable cervix (modified Bishop score  $\geq 5$ ) the cesarean delivery rate was 21% in the electively induced group vs. 20% in the expectantly managed group ( $p = 0.84$ ). Similarly there was no significant difference in the cesarean rate for women with an unfavorable cervix (43% vs. 34%,  $p = .16$ ). This study calls into question the long-standing dogma that elective induction of labor prior to 41 weeks increases the frequency of cesarean delivery.

With regard to long-term outcomes of the offspring, there has not been consistent evidence that oxytocin use results in neurodevelopmental disorders.<sup>32-35</sup> Moreover, as with many studies about labor induction, the studies that have assessed associations between intrapartum oxytocin use and neurodevelopmental outcomes have had several fundamental methodological flaws. For example, women are often induced for indications which themselves may be associated with adverse neurodevelopmental outcomes; in such a case of “confounding by indication”, adequate adjustment for the confounding factors may be difficult if not impossible. There is not evidence that elective induction (i.e., an induction without an underlying medical or obstetric indication) specifically is associated with adverse long-term neurodevelopmental

outcomes. Moreover, these studies have typically evaluated women undergoing induction versus those undergoing spontaneous labor; this comparison is inappropriate and not clinically relevant,<sup>36</sup> as spontaneous labor is not a choice but an event. Indeed, many women who are not “induced” at a given gestational age will ultimately require induction or oxytocin augmentation at a later gestational age, or experience an obstetric complication which itself may be associated with a risk of adverse neurodevelopmental outcome, a risk that may have been prevented had the women been induced earlier. Thus, the clinically meaningful comparison is labor induction versus expectant management. Yet, there are no data that suggest that elective induction compared with expectant management increases the risk of neurodevelopmental disorders or other adverse long-term outcomes.

**Table 3. Randomized Controlled Trials of Elective Induction of Labor (EIOL) at 39-40 Weeks vs Expectant Management (EM)**

Year and Reference	N	Patient Population (% nullips)	Gestational Age at EIOL	Gestational Age for EM	Outcome: EIOL vs. EM (p>0.05 unless noted)
1975 <sup>37</sup>	228	• Multiparous or nulliparous (46%)	39-40 weeks	41 weeks	Cesarean: 4.5% vs 7.7%
1978 <sup>38</sup>	230	• Multiparous or nulliparous*	39 weeks	42 weeks	Cesarean: 4.3% vs 1% Operative vaginal delivery: 18.5% vs 20.7%
1979 <sup>39</sup>	112	• Multiparous or nulliparous (45%)** • Favorable cervix	40 weeks	42 weeks	Operative vaginal delivery: 2.3% vs 4.8%
1989 <sup>40</sup>	345	• Multiparous or nulliparous (54%) • Favorable cervix	40 weeks	42 weeks	Nulliparas: Cesarean: 1.0% vs 3.4% Operative vaginal delivery: 3.0% vs 3.4% Multiparas: Cesarean: 1.2% vs 0% Operative vaginal delivery: 1.2% vs 0%
1999 <sup>40</sup>	194	• Nulliparous†	39 weeks	42 weeks	Cesarean: 6.4% vs 5.6% Operative vaginal delivery: 53.4% vs 33.3% (p=.03)
2005 <sup>41</sup>	226	• Multiparous or nulliparous (45%) • Favorable cervix	39-40 weeks	42 weeks	Nulliparas: Cesarean: 13.3% vs 10.3% Multiparas: Cesarean: 2.8% vs 3.8%

\* Excluded women in EIOL group who had spontaneous labor before 39 weeks and women in EM group if failed to go into spontaneous labor by 42 weeks

\*\* Excluded women in either group with spontaneous labor before 40 weeks or who required a cesarean

† Excluded women in EIOL group who had spontaneous labor before 39 weeks and women in EM group if induced before 42 weeks or failed to go into spontaneous labor by 42 weeks

#### 2.4.1 Randomized Trials of Elective Induction at Term versus Expectant Management

There have been several small randomized clinical trials comparing elective induction of labor at 37-40 weeks' gestation with expectant management until 41-42 weeks (Table 3).<sup>37-42</sup> None of these studies found an increased frequency of cesarean section among induced participants. However, these trials have significant limitations. First, all were underpowered to detect the magnitude of increase in cesarean rate that would be considered clinically relevant. In addition, because two trials only included women with a favorable Bishop score, the generalizability of the data to women with an unfavorable score is limited.

Nevertheless, meta-analysis of these data generated by randomized trials reveals a reduction in the frequency of cesarean section with induction (RR 0.89; 95% CI 0.81 to 0.97).<sup>2</sup> Although it did not address elective induction, the Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT), a randomized trial comparing induction to expectant management for women with hypertensive disease of pregnancy, also demonstrates that labor induction may not increase the risk of cesarean (14% in the induction of labor group versus 19% in the expectant management group (RR 0.75; 95% CI 0.55-1.04).<sup>43</sup>

## **2.5 Rationale for a Randomized Clinical Trial**

Given the reported increased risks of adverse events in pregnancies extending beyond 39 weeks it has been hypothesized that a policy of planned elective induction at 39 weeks could improve outcomes for the infant and the mother. For multiparous patients, especially those with a favorable cervix, it is perhaps easy to justify an elective induction at 39 weeks given the low risk of cesarean section. However, for nulliparous patients the current evidence, derived mainly from retrospective observational studies, does not allow a clear recommendation. Nevertheless, a trend towards an increased rate of elective labor induction in pregnancies at 39 weeks has been reported, indicating that practitioners are more commonly using elective induction at this gestational age,<sup>43</sup> even as others caution against routine elective induction prior to 41 weeks given the reported increased risk of cesarean delivery.<sup>19,44,45,46</sup> Ultimately, a randomized controlled trial is necessary to satisfactorily understand whether elective induction of labor of nulliparas at 39 weeks improves neonatal and maternal outcomes.

## 3 Study Design

### 3.1 Primary Research Question

This randomized trial will address the primary research question: does elective induction of labor in nulliparous women at 39 weeks improve perinatal outcome compared with expectant management?

### 3.2 Secondary Research Questions

Secondary research questions this study will address are:

- Does elective induction of labor in nulliparous women at 39 weeks reduce the risk of any of the maternal outcomes listed in Section 4.7.2?
- Does elective induction of labor in nulliparous women at 39 weeks modify the patient-centered outcomes listed in section 4.7.2?
- Does elective induction of labor in nulliparous women at 39 weeks reduce the risk of any of the fetal and neonatal outcomes listed in section 4.7.3?
- Does elective induction of labor in nulliparous women at 39 weeks modify the utilization of the medical resources listed in section 4.7.4?
- Does the proposed effect of elective induction of labor in nulliparous women at 39 weeks vary according to any of the subgroups listed in section 5.5?

### 3.3 Design Summary

The study is a randomized controlled multi-center clinical trial of 6000 women at 38 weeks 0 days to 38 weeks 6 days randomized to one of two arms at participating MFMU Network clinical centers.

- Elective induction of labor between 39 weeks 0 days and 39 weeks 4 days
- Expectant management (unless a medical indication arises) until at least 40 weeks 5 days.

### 3.4 Eligibility Criteria

#### 3.4.1 Inclusion Criteria

1. Nulliparous - no previous pregnancy beyond 20 weeks
2. Singleton gestation. Twin gestation reduced to singleton, either spontaneously or therapeutically, is not eligible unless the reduction occurred before 14 weeks project gestational age (see below).
3. Gestational age at randomization between 38 weeks 0 days and 38 weeks 6 days inclusive based on clinical information and evaluation of the earliest ultrasound as described in Gestational Age Determination in Section 3.4.2 below.

#### 3.4.2 Gestational Age Determination

Gestational age is determined in the following manner, and is denoted “project gestational age”. The “project EDC”, which is based on the project gestational age, cannot be revised once a determination has been made. If the pregnancy is conceived by in-vitro fertilization, project gestational age is calculated from the date of embryo transfer and the embryo age at transfer. If the pregnancy is conceived spontaneously (including ovulation induction and artificial insemination) information from the earliest

dating ultrasound and the last menstrual period are used to determine project gestational age. The following algorithm is used:

- The first day of the last menstrual period (LMP) is determined, and a judgment made as to whether or not the patient has a “sure” LMP date.
- If the LMP date is unsure, measurement(s) obtained at the patient’s first dating ultrasound examination is used to determine the project gestational age. The first dating ultrasound must have been conducted before 14 weeks 0 days by crown rump length.
- If the LMP date is sure, project gestational age is determined by a comparison between the gestational age by LMP and by the earliest dating ultrasound. The first dating ultrasound must have been conducted before 21 weeks 0 days by LMP. If the ultrasound confirms the gestational age by LMP as in the table below, the LMP-derived gestational age is used to determine the project gestational age. Otherwise, project gestational age will be determined based upon the ultrasound measurement.

**Table 4. Cutoffs for Using LMP to Determine Gestational Age for Sure LMP**

<b>Gestational age at first ultrasound by LMP</b>	<b>Ultrasound agreement with LMP</b>
Up to 13 weeks 6 days	± 5 days
Up to 20 weeks 6 days	± 10 days

### **3.4.3 Exclusion Criteria**

1. Project gestational age at date of first ultrasound is > 20 weeks 6 days
2. Plan for induction of labor prior to 40 weeks 5 days
3. Plan for cesarean delivery or contraindication to labor
4. Signs of labor (regular painful contractions with cervical change)
5. Fetal demise or known major fetal anomaly
6. Heparin or low-molecular weight heparin during the current pregnancy
7. Placenta previa, accreta, vasa previa
8. Active vaginal bleeding greater than bloody show
9. Ruptured membranes
10. Cerclage in current pregnancy
11. Known oligohydramnios, defined as AFI < 5 or MVP < 2
12. Fetal growth restriction, defined as EFW < 10<sup>th</sup> percentile
13. Known HIV positivity because of modified delivery plan
14. Major maternal medical illness associated with increased risk for adverse pregnancy outcome (for example, any diabetes mellitus, lupus, any hypertensive disorder, cardiac disease, renal insufficiency)
15. Refusal of blood products
16. Participation in another interventional study that influences management of labor at delivery or perinatal morbidity or mortality
17. Delivery planned elsewhere at a non-Network site

### **3.5 *Informed Consent Criteria***

Each center will develop its own consent forms according to the requirements of its own institutional review board using the model consent form in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form will be provided to the patient.

Women who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded.

### **3.6 *Randomization Method***

Randomization for consenting women will occur at 38 weeks 0 days to 38 weeks 6 days of gestation. Consenting women will be assigned to induction of labor at 39 weeks 0 days to 39 weeks 4 days or expectant management in a 1:1 ratio according to a randomization sequence prepared and maintained centrally by the Biostatistical Coordinating Center (BCC).

The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease.<sup>47</sup> Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences in the clinic populations and possible differences in patient management.

## 4 Study Procedures

### 4.1 Screening for Eligibility and Consent

All nulliparous women with a singleton gestation between 34 and 38 weeks are potentially eligible for screening. Inclusion/exclusion criteria will be reviewed with the patient's chart.

If a patient appears to meet the criteria for the trial, she will be told about the study and asked for written informed consent to participate in the trial. Consent may be obtained anytime from 34 weeks 0 days to 38 weeks 6 days of gestation.

Each patient must undergo a digital cervical exam between 72 hours prior to randomization and 24 hours after randomization. The three components of the modified Bishop score must be obtained during this exam. Table 5 provides the scoring system that uses the following three components to derive the modified Bishop score:

- Cervical dilation
- Cervical length or effacement
- Fetal station

**Table 5. Scoring System for the Modified Bishop Score**

Station (in relation to the spines)	-3 cm	-2 cm	-1 - 0 cm	1 - 2 cm
	0	1	2	3
Dilation (of the cervix)	0 cm	1-2 cm	3-4 cm	>4 cm
	0	2	4	6
Length (of the cervix)	3 cm	2 cm	1 cm	0 cm
	0	1	2	3

### 4.2 Randomization

Eligibility should be verified again before randomization. Eligible and consenting patients will be randomized by certified research staff using an internet based randomization system maintained by the BCC. Randomization will occur when the patient is from 38 weeks 0 days to 38 weeks 6 days of gestation. The patient will be assigned either to the induction of labor group or the expectant management group.

If the patient has had a digital cervical exam within the past 72 hours, and all components of the modified Bishop score are documented (cervical dilation, cervical effacement or cervical length, and fetal station), randomization may be done in person or over the telephone. If the patient has not had a digital cervical exam within the past 72 hours, or if components of the modified Bishop score are not documented, she must be randomized in person and have a digital cervical exam within that same day.



### **4.3 Baseline Procedures**

In addition to information collected for eligibility, project gestational age, and project EDC determination, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Components of the modified Bishop score: cervical dilation, cervical length or effacement, and fetal station from digital cervical exam
- Demographic information: age, race, ethnicity, insurance status
- Medical history: first clinic weight, current weight, height, chronic disease history
- Obstetrical history including outcome(s) of any prior pregnancies
- Social history: marital status, alcohol use, and tobacco use
- Current pregnancy complications

### **4.4 Study Procedures**

Women randomized to induction of labor will undergo induction via oxytocin at 39 weeks 0 days to 39 weeks 4 days. Those with an unfavorable cervix (modified Bishop score < 5) will first undergo cervical ripening (method left to the discretion of the patient's physician) in conjunction with or followed by oxytocin stimulation unless a contraindication arises.

Women randomized to expectant management will have at least weekly follow-up visits with their providers and, unless a medical indication is present, will continue pregnancy until at least 40 weeks 5 days of gestation. Antepartum fetal testing will be initiated no later than 41 weeks 6 days according to policies at each center. All patients will undergo induction via oxytocin by 42 weeks 2 days.

### **4.5 Patient Management and Follow-up**

Patients in the induction of labor group (as well as patients in the expectant management group that undergo induction of labor) should be allowed adequate time to labor before considering the induction "failed" and proceeding to cesarean section. An induction will be considered "failed" if at least 12 hours have elapsed since both rupture of membranes and use of a uterine stimulant and the patient remains in latent labor. It is expected that the fetal heart rate will be monitored while the patient is being induced (including ripening) and during labor and that patients will stay in the hospital until delivery once the induction (including ripening) is started. Mechanical ripening using a Foley catheter without saline infusion is permitted without monitoring and may be used in an outpatient setting according to policies at each center.

For patients in the expectant management group, only a valid medical indication should warrant delivery before 40 weeks and 5 days. Otherwise, no attempt will be made to alter or mandate clinical management of the subjects.

Women will be asked about pain experienced during childbirth and asked to complete a questionnaire on feelings of control during childbirth. All women will be contacted at six weeks postpartum to determine unanticipated outpatient or inpatient visits for them or their infants since discharge and to complete the same questionnaire about feelings of control again.

## **4.6 Adverse Event Reporting**

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol.

The NICHD Program Scientist and the BCC will be notified within seventy-two hours of any maternal death, perinatal death, or life-threatening maternal event by email/phone/fax, if the event occurred in a MFMU Network hospital. For any maternal death, perinatal death, or life-threatening maternal event occurring outside a MFMU Network hospital, the adverse event must be reported to the NICHD and the BCC within twenty-four hours of being notified. These and other adverse events deemed serious, unexpected and definitely, possibly or probably related, will be immediately (within twenty-four hours of notification) forwarded by the BCC to the DSMC Chair, NIH representative, and any other DSMC member who requests notification. If a death is reported, a copy of the patient's medical record will be made.

Adverse events which do not qualify under the above definition must be reported to the BCC within 7 days of being notified. These adverse events will be collected and sent to the Chair, NIH representative, and any other requesting DSMC member on a monthly basis. The Chair decides whether the adverse event reports should be disseminated to the rest of the committee, and whether a follow-up call or meeting is required. NICHD representatives may also request follow-up of specific events. All adverse events will be considered along with other interim safety data in the DSMC deliberations.

## **4.7 Study Outcome Measures and Ascertainment**

### **4.7.1 Primary Outcome**

The primary outcome is a composite of severe neonatal morbidity and perinatal mortality (any one of the following):

- Antepartum, intrapartum, or neonatal death
- Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiorespiratory support within first 72 hours
- Apgar  $\leq 3$  at 5 minutes
- Neonatal encephalopathy as defined by Shankaran et al.<sup>48</sup>
- Seizures
- Sepsis. The diagnosis of sepsis will require the presence of a clinically ill infant in whom systemic infection is suspected with a positive blood, CSF, or catheterized/suprapubic urine culture; or, in the absence of positive cultures, clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection.
- Pneumonia confirmed by X-ray or positive blood culture.
- Meconium aspiration syndrome
- Birth trauma (bone fractures, brachial plexus palsy, other neurologic injury, retinal hemorrhage facial nerve injury)
- Intracranial hemorrhage or subgaleal hemorrhage
- Hypotension requiring pressor support

#### **4.7.2 Maternal Secondary Outcomes**

1. Cesarean delivery and indication
2. Incisional extensions at cesarean section, including J shape or T shape; or cervical traumas
3. Operative vaginal delivery and indication
4. Chorioamnionitis, defined as a clinical diagnosis before delivery
5. Third or fourth degree perineal laceration
6. Maternal death
7. Admission to intensive care unit (ICU)
8. Preeclampsia/gestational hypertension
9. Postpartum hemorrhage, defined as any of the following:
  - a. Transfusion
  - b. Non-elective hysterectomy
  - c. Use of two or more uterotonics other than oxytocin
  - d. Other surgical interventions such as uterine compression sutures, uterine artery ligation, embolization and hypogastric ligation, balloon tamponade
  - e. Curettage
10. Patient-reported outcomes including feelings of control during childbirth, as measured by the Labour Agency Scale,<sup>49</sup> and two questions regarding pain experienced during childbirth using a visual analog scale<sup>50</sup>
11. Interval from randomization to delivery
12. Gestational age at delivery
13. Maternal postpartum infection, defined as any of the following:
  - Clinical diagnosis of endometritis
  - Wound reopened for hematoma, seroma, infection or other reasons
  - Cellulitis requiring antibiotics
  - Pneumonia
  - Pyelonephritis
  - Bacteremia unknown source
  - Septic pelvic thrombosis
14. Maternal venous thromboembolism (deep venous thrombosis or pulmonary embolism)

#### **4.7.3 Fetal and Neonatal Secondary Outcomes**

1. Birth weight, macrosomia > 4500 g, large for gestational age (LGA) defined as > 90<sup>th</sup> percentile weight for gestational age, assessed specifically by sex and race of the infant based on United States birth certificate data<sup>51</sup>
2. Duration of respiratory support including ventilator, CPAP, high-flow nasal cannula (HFNC)

3. Small for gestational age defined as  $< 5^{\text{th}}$  and  $< 10^{\text{th}}$  percentile weight for gestational age, assessed specifically by sex and race of the infant based on United States birth certificate data<sup>51</sup>
4. Cephalohematoma
5. Shoulder dystocia
6. Transfusion of blood products or blood
7. Hyperbilirubinemia requiring phototherapy or exchange transfusion
8. Hypoglycemia (glucose  $< 40$  mg%) requiring IV therapy
9. Admission to neonatal intensive care unit (NICU) or intermediate care unit

#### **4.7.4 Utilization of Medical Resources**

1. Number of clinic visits post randomization to admission for delivery
2. ER/urgent care/triage visits post randomization to delivery
3. Non-stress tests, biophysical profiles (BPPs), modified BPPs, ultrasounds done other than BPP, Doppler, contraction stress tests
4. Epidural use
5. Intrauterine pressure catheter (IUPC) or fetal scalp electrode placement
6. Use of induction and ripening agents, maximum dose of oxytocin
7. Antepartum hospital admission
8. Number of hours on the labor and delivery unit
9. Maternal postpartum length of hospital stay
10. Neonatal length of hospital stay
11. Length of neonatal intensive care unit or intermediate care stay
12. Post discharge resource utilization including inpatient and outpatient visits for mother or baby

## 5 Statistical Considerations

### 5.1 Data Relevant to the Primary Outcome

To estimate the rate of the primary outcome in the expectant management group, data from the MFMU Network's APEX study were evaluated. APEX was an observational study of approximately one-third of all deliveries at 25 hospitals in the MFMU Network, collected over a three-year period. For this analysis only nulliparous women with a singleton pregnancy delivered at 39 weeks 0 days to 42 weeks 0 days were included; those with diabetes, hypertension before 38 weeks, previa and abruption were excluded, yielding a cohort of 24,683 women. A composite outcome as close as possible to the proposed composite primary outcome for this trial was evaluated in these women. However, APEX only included pregnancies with fetal heart tones on admission for delivery and therefore stillbirth would be slightly underestimated. In addition, presence of thick meconium was used as a surrogate for meconium aspiration syndrome. The outcome rate in this cohort was 2.3% excluding presence of thick meconium; with thick meconium present the outcome rate was 9.3%. The real primary outcome rate could be expected to be between these two estimates.

Also, among women in the FOX trial, risks of adverse neonatal outcome at term (neonatal composite outcome including death, respiratory distress, seizure, sepsis, intubation and ventilator support, 5 minute Apgar score of 3 or less or hypoxic ischemic encephalopathy) were 3.7% at 36-38 weeks, 3.5% at 39 weeks, 3.8% at 40 weeks and 5.0% at  $\geq 41$  weeks.<sup>38</sup>

Therefore the neonatal composite outcome rate for pregnancies expectantly managed beyond 39 weeks would be expected to be between 3.5% and 5%. This is consistent with other literature presented in Chapter 1.

### 5.2 Sample Size and Power

#### 5.2.1 Primary Outcome

Table 6 shows the sample sizes per group (rounded up to the next 10) to detect a 35-40% reduction in the primary outcome, with 80% to 90% power, assuming type I error of 5% 2-sided and primary outcome rate in the expectant management arm between 3.5% and 5%. Some women will labor after randomization but prior to when their randomized assignment could be implemented (i.e., before 39 weeks). In addition, some women may undergo an elective induction off-protocol before 40 weeks, 5 days without a specific indication. These 'crossovers' would therefore behave more like the elective induction group; and it is assumed that their primary outcome rate would be the same as that of the elective induction group. This has the effect of reducing the effect size slightly depending on the proportion of crossovers: for example with 5% crossovers, the 40% nominal reduction becomes 39%.

Sample sizes were adjusted to take into account that between 5 and 10% of the women in the expectant management group will behave more like the elective induction group. The actual effect sizes are shown in parentheses in the table.

Data from observational studies suggest that a policy of induction of labor at 39 weeks may result in an equivalent reduction in adverse outcome.<sup>6, 46</sup> Using a type I error of 5% 2-sided and power of 85%, and an estimate that 7.5% of women in the expectant management group will be crossovers, 3000 women in each group (total N= 6000) would be needed to detect the actual reduction in primary outcome of 38%.

If the primary outcome rate is as high as 5%, a sample size of 6000 patients is sufficient to detect a 33-34% reduction in the primary outcome with at least 85% power, again assuming that 7.5% of women will be crossovers.

**Table 6. Sample Sizes per Group for Different Primary Outcome Rates, Power and Effect Sizes**

Reduction in Primary Outcome Rate (Reduction Adjusted for Crossover)	Power %	Nominal Primary Outcome Rate in Expectant Management Group			
		3.5%	4.0%	4.5%	5.0%
0% Crossover					
35% (35%)	80	3030	2650	2350	2120
	85	3460	3030	2690	2420
	90	4050	3540	3150	2840
40% (40%)	80	2250	1970	1750	1570
	85	2570	2250	2000	1800
	90	3010	2630	2340	2110
5% Crossover					
35% (33.8%)	80	3320	2900	2580	2320
	85	3790	3320	2950	2660
	90	4440	3880	3450	3110
40% (38.8%)	80	2460	2150	1910	1720
	85	2810	2460	2190	1970
	90	3290	2880	2560	2300
7.5% Crossover					
35% (33.2%)	80	3480	3040	2710	2440
	85	3980	3480	3100	2790
	90	4660	4070	3620	3260
40% (38.1%)	80	2580	2260	2010	1810
	85	2950	2580	2290	2060
	90	3450	3020	2680	2420
10% Crossover					
35% (32.6%)	80	3650	3200	2840	2560
	85	4180	3660	3250	2930
	90	4890	4280	3810	3430
40% (37.5%)	80	2700	2370	2100	1890
	85	3090	2710	2410	2170
	90	3620	3170	2820	2530

### 5.2.2 Cesarean Delivery

Assuming that the rate of cesarean delivery is 30% in the expectant management group, a sample size of 6000 women also yields more than 90% power to detect a nominal 15% increase or decrease even after adjusting for 7.5% crossovers.

### **5.3 Feasibility**

Given that the sample size estimates are based on a composite of rare outcomes, it is planned that the primary outcome rate in the expectant management group be examined in the first 1000 patients. These data would be presented to the DSMC before any comparison by group, and the committee would be charged with making a recommendation regarding potential revision of the sample size in addition to addressing the feasibility of answering the primary research question.

### **5.4 Interim Analysis**

The Data and Safety Monitoring Committee (DSMC) meets in person at least once per year and more often if recommended by the committee. Before each of the annual meetings, a formal detailed report will be written by the Biostatistical Coordinating Center (BCC) which presents all baseline variables, protocol adherence, side effects, all adverse events reported, as well as center performance in terms of recruitment, data quality, loss to follow-up and protocol violations.

Once sufficient patients have been accrued into the trial, the report will also include a formal interim analysis evaluating the primary outcome by treatment group. For this evaluation, a cohort of patients is chosen consisting of all patients randomized before a certain date so that the analysis cohort does not depend on gestational age at delivery.

The main statistical issue relevant to interim analysis is the problem of performing multiple tests of significance on accumulating data. For this trial, the group sequential method of Lan and DeMets will be used to characterize the rate at which the type I error is spent.<sup>52</sup> This method is flexible with regard to the timing of the interim analyses. Asymmetric stopping boundaries will be used for the Lan-deMets procedure. The upper boundary which describes the stopping rule for benefit will be based on 1-sided type I error of .025 and the Lan-deMets generalization of the O'Brien-Fleming boundary.

The lower boundary will be based on a less stringent stopping rule: 1-sided type I error of .05 and the Lan-deMets generalization of the Pocock type boundary.

It is often useful to calculate conditional power given the observed data to date, and conditional on the future data showing the originally assumed design effect. If this conditional power is low (under 10 percent) the DSMC may consider termination for futility if the accrual rate is slow, with confidence that the Type II error is not greatly inflated.<sup>53</sup>

It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.

### **5.5 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, all relevant data available from each patient will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of compliance.

The primary analysis will consist of a simple comparison of binomial proportions. The relative risk and confidence interval will be reported. The individual components of the composite outcome will also be examined. If the treatment groups are found to differ on a pre-treatment factor known to be a risk factor for the outcome, the statistical analysis will adjust for these differences. An evaluation of treatment by center interaction will be included. An analysis adjusting by center also will be performed to ensure that center differences do not change the conclusion.

If the two groups show a difference in the incidence of the primary outcome, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout particular

subgroups of patients. Indeed, NIH guidelines require investigators to evaluate consistency between the genders and across racial subgroups (see Section 5.5.1). It should be noted, however, that subgroup analyses have been greatly abused, particularly when there is no overall treatment difference.<sup>54</sup> There is a strong temptation to search for a specific subpopulation in which the therapy is nevertheless effective. Yusuf et al. concluded “*the overall ‘average’ result of a randomized clinical trial is usually a more reliable estimate of the treatment effect in the various subgroups examined than are the observed effects in individual subgroups.*”<sup>55</sup> Thus subgroup analyses will be interpreted with care.

It is generally acknowledged that subgroup analysis that is pre-specified in the protocol has more validity than ad-hoc comparisons. The following factors will be considered for subgroup analysis, if there is a significant interaction between the factor of interest and the treatment effect.

- Race/ethnicity (see below)
- Modified Bishop score ( $< 5$  and  $\geq 5$ )
- Body mass index (obese and non-obese)

Loss to follow-up will be defined as no information regarding stillbirth or neonatal outcome. There should be a low loss to follow-up rate. It is possible that a woman would deliver at a non-Network hospital; however, a record release will be obtained at enrollment to ensure that delivery and neonatal information can be obtained. However, to determine whether the results are robust, a sensitivity analysis will be performed including patients lost to follow up with different assumptions regarding their outcome.

Since many of the secondary endpoints are dichotomous variables like the primary outcome, standard statistical methods for rates and proportions will be appropriate. The Wilcoxon rank sum test will be used to compare continuous variables, and survival analysis methodology may be used to compare time-to-event variables.

In general, analyses of data will be conducted to address the primary and secondary research questions of the trial, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study.

### **5.5.1 Racial/Ethnic Subgroup Analysis**

The racial/ethnic composition of patients of women recruited into the MFMU Network trials varies. Assuming for this trial that the composition is 25% African-American and 30% Hispanic, similar to the ongoing STAN trial, there is limited power (40-50%) to detect a 50% reduction in the primary outcome in the separate subgroups.



## 6 Data Collection

### 6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- AR01 Screening Log.
- AR02 Eligibility and Randomization Form is completed for all patients eligible and consenting for the study, and documents the project gestational age and randomization digital cervical exam.
- AR04 Baseline Form is completed for all randomized patients. This form includes detailed demographic and social data, and medical and obstetrical history.
- AR05 Clinic and Hospital Visit Log documents scheduled and unscheduled clinic, urgent care and hospital visits, procedures and diagnostic tests, including the antepartum portion of the delivery admission.
- AR08 Labor and Delivery Summary Form documents specific pregnancy complications since randomization, in addition to labor, delivery and postpartum information.
- AR08A Labour Agency Questionnaire
- AR09 Neonatal Baseline Form records date and time of birth, delivery data and status at delivery, for each fetus/infant.
- AR10 Neonatal Outcome Form records outcome data for all infants admitted to the NICU or special care nursery.
- AR11 Patient Status Form documents loss to follow up/withdrawal status, last date of contact for lost to follow-up patients.
- AR12 Adverse Event Form records serious and non-serious adverse events.
- AR13 Postpartum Follow-up Form
- AR13A Maternal Follow-up Log documents the reasons and diagnoses associated with maternal clinic, urgent care and hospital visits
- AR13B Infant Follow-up Log documents the reasons and diagnoses associated with infant clinic, urgent care and hospital visits

### 6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

### 6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is

generated in MIDAS for initial review by BCC staff, who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

#### **6.4 Performance Monitoring**

The BCC will present regular reports to the ARRIVE Subcommittee, the Steering Committee, and the Data and Safety Monitoring Committee. These include:

- Monthly Recruitment Reports - reports of the number of women screened and enrolled by month and by clinical center are provided monthly to the ARRIVE Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the ARRIVE Subcommittee and all other members of the Steering Committee.
- Data and Safety Monitoring Committee Reports - 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 safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

## 7 Study Administration

### 7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of fourteen clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

#### 7.1.1 Participating Clinical Centers

The participating Principal Investigators of the clinical 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 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC 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 protocols, administration and conduct of the studies and preparation of publications.

#### 7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with research being conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Program Scientist convenes and attends the meetings.

### 7.2 Committees

#### 7.2.1 Steering Committee

This committee consists of seventeen members. The Principal Investigator from each of the fourteen clinical centers, the BCC, and the NICHD MFMU Network Program Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

#### 7.2.2 Protocol Subcommittee

The subcommittee consists of a chair (who is an investigator from one of the clinical centers), investigators from one or more other clinical centers, BCC staff, nurse coordinators, outside consultants

(if appropriate), and the NICHD Network Program Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

### **7.2.3 Publications Committee**

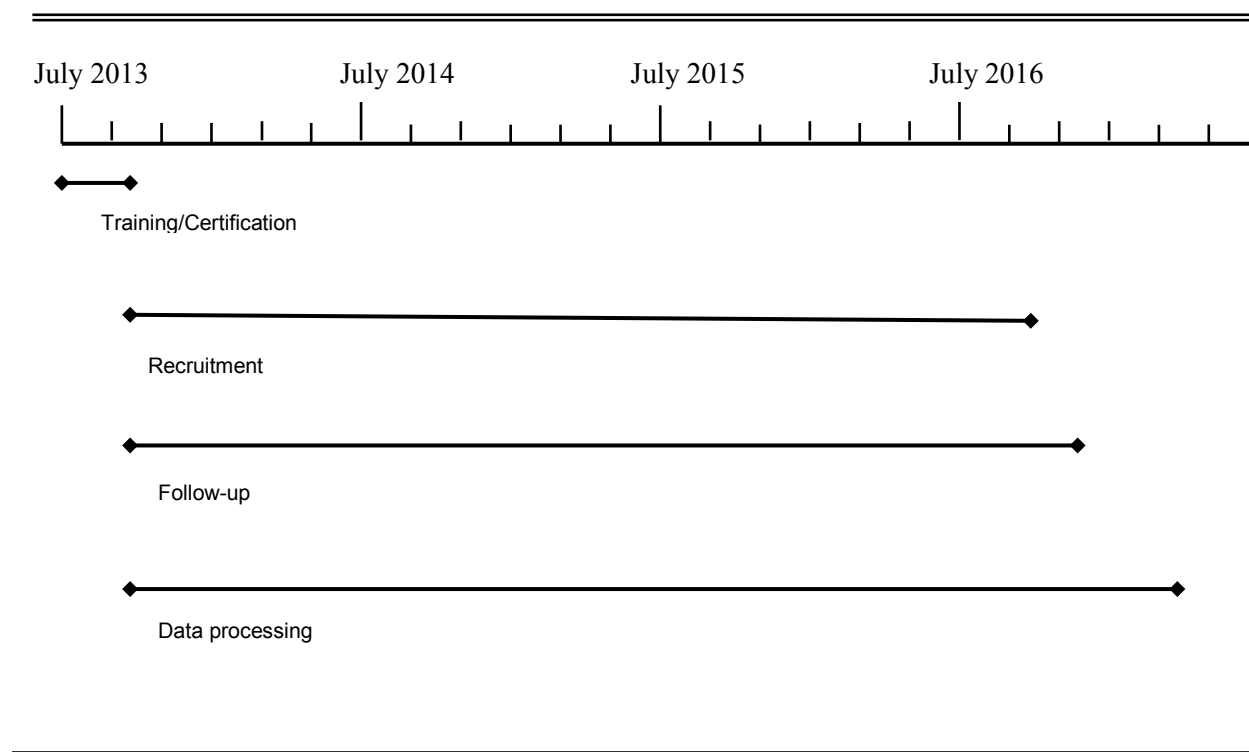
The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

### **7.2.4 Data and Safety Monitoring Committee**

The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD. Before the trial can begin, the protocol must be approved by the committee. During the conduct of the study, the committee is charged with monitoring the emerging results for efficacy and safety, in addition to center performance and protocol adherence. Recommendations by the committee can include protocol modification, early termination for efficacy, or for unexpected safety problems. Recommendations are made to the NICHD and disseminated to the Steering Committee.

## 8 Study Timetable

Figure 1. Timetable



### 8.1 Training and Certification

During the study start-up period, preparation of the final case report forms, manual of operations, and randomization sequence, in addition to implementation of the data entry and management system will take place. Training will be held with the nurse coordinators in July and October 2013, with a projected study start date of October 2013. Each participating center must be certified to start the trial before recruitment at that center can begin. The certification requirements are designed to ensure that personnel involved in the trial are committed to the study and proficient in study procedures, and that the center has satisfied regulatory requirements. Each center is required to obtain IRB approval for the study before they are certified to begin the trial.

### 8.2 Recruitment and Data Collection Period

Approximately 160,000 women deliver at MFMU Network centers annually. The APEX study database was queried to determine what proportion of all deliveries would be eligible for ARRIVE. A total of 17,960 pregnancies out of 115,502 or 15.5% satisfied the eligibility criteria. In addition, a pilot survey was conducted at four of the MFMU Network centers. A total of 204 women were queried to find out whether they would consent to this trial if it were presented to them. A total of 55% responded 'yes', 13% responded 'maybe' and 32% responded 'no'. Assuming only 20% percent of the 160,000 deliveries are available (due to, for example, certain sites or care providers not participating), 15.5% satisfying eligibility criteria and a 55% consent rate, this translates to 2700 patients per year. Assuming no limit on the ability to schedule inductions at 39 weeks, the study would easily be completed within 30 months.

Allowing an additional six months (i.e., 3 years in total), with only 30 of the 36 sites participating, translates to 67 patients per year per hospital (1.3 women per hospital per week) which should be feasible. Thus the overall recruitment goal is 167 women per month.

### **8.3 *Final Analysis***

After a two-month period for completion of data entry for the trial and close-out of the delivery and primary outcome, the data set will be locked and available for the primary and other main analyses.

## Appendix A Design Summary

### Induction in Nulliparous Women at 39 Weeks to Prevent Adverse Outcomes: A Randomized Controlled Trial

**OBJECTIVE:** To determine whether elective induction of labor in nulliparous women at 39 weeks improves adverse perinatal/neonatal outcome compared with expectant management.

<b>ORGANIZATION</b>		<b>SCHEDULED EVALUATIONS / DATA COLLECTION</b>	
Clinical Centers:	UAB, Ohio State, UTSW, Utah, Brown, Columbia, Case Western, UT-Houston, UNC, Northwestern, UTMB-Galveston, Colorado, Duke, Stanford	Randomization:	<ul style="list-style-type: none"> <li>❖ Gestational age estimation</li> <li>❖ Digital cervical exam; Bishop score</li> <li>❖ Pregnancy, exposure and medical history</li> </ul>
Subcommittee:	William Grobman, MD (Chair)	Post-randomization:	<ul style="list-style-type: none"> <li>❖ Weekly visit with provider (expectant management group)</li> </ul>
<b>DESIGN</b>		Delivery:	<ul style="list-style-type: none"> <li>❖ Patient-centered outcomes questionnaire</li> <li>❖ Delivery and neonatal data</li> <li>❖ Central chart review for primary outcome</li> </ul>
Major Eligibility Criteria:	<ul style="list-style-type: none"> <li>❖ Singleton gestation</li> <li>❖ Gestational age 38<sup>0</sup> to 38<sup>6</sup> wks</li> <li>❖ Nulliparous</li> </ul>	Postpartum:	<ul style="list-style-type: none"> <li>❖ Patient-centered outcomes questionnaire</li> </ul>
		<b>MANAGEMENT PROTOCOL</b>	
Groups:	<ul style="list-style-type: none"> <li>❖ Induction of labor at 39 weeks</li> <li>❖ Expectant management with induction by 42 weeks, if undelivered</li> </ul>	Induction Group	<ul style="list-style-type: none"> <li>❖ Induction via oxytocin at 39<sup>0</sup>-39<sup>4</sup> wks.</li> <li>❖ If unfavorable cervix (modified Bishop score &lt; 5) start with cervical ripening</li> </ul>
Random Allocation:	Standard urn design; 1:1 allocation	Expectant Mgmt Group	<ul style="list-style-type: none"> <li>❖ Continue pregnancy until at least 40<sup>5</sup> wks (unless indication for delivery)</li> <li>❖ Start antepartum fetal testing no later than 41<sup>6</sup></li> <li>❖ All patients induced by 42<sup>2</sup> wks</li> </ul>
Level of Masking:	Unmasked	<b>OUTCOME MEASURES</b>	
Stratification:	<ul style="list-style-type: none"> <li>❖ Clinical site</li> </ul>	Primary:	<ul style="list-style-type: none"> <li>❖ Neonatal adverse outcome/fetal death</li> </ul>
Sample Size:	<ul style="list-style-type: none"> <li>❖ 6000</li> </ul>	Major Secondary:	<ul style="list-style-type: none"> <li>❖ Cesarean delivery</li> <li>❖ Maternal adverse outcomes</li> <li>❖ Gestational age at delivery</li> <li>❖ Patient centered outcomes</li> <li>❖ Utilization of medical resources</li> </ul>
Assumptions:	<ul style="list-style-type: none"> <li>❖ Outcome event=perinatal death /neonatal adverse outcome</li> <li>❖ Expectant management event rate = 3.5%</li> <li>❖ Induction of labor group event rate = 2.28% (38% reduction)</li> <li>❖ Type 1 error = 5% two sided</li> <li>❖ Power =85%</li> </ul>	<b>TIMETABLE</b>	
Interim Analysis:	<ul style="list-style-type: none"> <li>❖ Lan-DeMets group sequential method</li> </ul>	Enrollment	<ul style="list-style-type: none"> <li>❖ Oct 2013 to Sep 2016</li> </ul>
		Data Collection	<ul style="list-style-type: none"> <li>❖ Oct 2013 to Nov 2016</li> </ul>
		Closeout	<ul style="list-style-type: none"> <li>❖ Dec 2016 to Mar 2017</li> </ul>

## **Appendix B    Sample Informed Consent Form**

**Research Study Title:** A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

**Sponsor:** Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

**Principal Investigator:** \_\_\_\_\_ **Phone** (\_\_\_\_) \_\_\_\_ - \_\_\_\_

### **Introduction**

You are invited to take part in a research study. This consent form provides the information about the risks and benefits of the study. A member of the research team is available to answer your questions and to provide further explanations. You are free to choose whether or not you will take part in the study. If you agree to take part in the research, you will be asked to sign this consent form. This process is known as informed consent.

### **Research Purpose**

You are being invited to participate because you are pregnant, having your first baby, and are planning to labor. The goal of the study is to determine whether coming to the hospital and having your labor started with medicine (i.e., labor induction) at 39 weeks of pregnancy can improve the baby's health at birth when compared with waiting for labor to start on its own.

Many doctors wait until 41 weeks for labor to start on its own. However, some studies, but not all, have shown that being induced at 39 weeks of pregnancy may improve the baby's outcome. Some older studies have suggested a higher risk of cesarean, but other recent studies have not shown this increased risk. No studies like this one have been done before in the United States. This study is planning to enroll 6,000 women across the country. Half of the women will be induced at about 39 weeks of gestation and half will have the existing prenatal care (that is, waiting for start of labor).

### **Procedures**

If you consent to the study, when you are within one to two weeks of your due date, you will be randomized (like flipping a coin) to one of two groups. In one group (the "induction of labor" group), you will have your labor started through the use of medicine within a few days of reaching 39 weeks of pregnancy. Depending upon how open your cervix is (the cervix is the opening to your uterus or birth canal), your doctor will decide the best way to start your labor. In the other group (the "expectant management group") you will continue with your pregnancy until either you begin labor or your care provider determines that you need to be delivered or you reach 41-42 weeks of gestation (1-2 weeks after your due date).

Regardless of which group you are in, your care provider will check your cervix (the opening of your uterus or birth canal) during a pelvic examination. This may have already been done as a part of regular care within three days of your being randomized in which case it would not have to be repeated. If you receive medication to help open your cervix or start your labor, your baby's heart rate will be monitored all the time you are receiving the medication and when you are in labor. Once you receive medication to help open your cervix or start your labor you should expect to stay in the hospital until delivery. All other care during your pregnancy and during labor will be at the discretion of your care provider.

After delivery, research staff will review your medical chart for clinical and outcome information such as any treatments or medicines given during labor and whether you had a vaginal delivery or cesarean section. They will also review the medical chart of your newborn. The research team will collect information regarding your hospital course and that of your newborn until hospital discharge.



You will be asked two questions about the pain you experienced during childbirth and asked to fill out one questionnaire soon after your baby is born. The questionnaire will be about how you felt about the process of labor and giving birth. Six weeks after your baby is born, research staff will contact you to find out about any unplanned hospital or clinic visits for you or your baby and you will be asked to fill out the same questionnaire about the process of labor again.

### **Possible Risks**

During labor induction, the same types of complications that can occur during any labor can occur. At present, it is not known whether labor induction at 39 weeks is associated with a greater chance of cesarean delivery. Some older studies have suggested a higher risk of cesarean, but other recent studies have not shown this increased risk.

### **Benefits**

If you decide to take part in this research study, you and your baby may not directly benefit. Your participation may help doctors determine the best time to plan for delivery in the future.

### **Alternative Procedures**

The alternative to this study is not to participate. Women who do not take part in this study will continue with their pregnancies until either they begin labor or their care provider determines there is a reason that they need to be delivered before labor begins (i.e., the standard care during pregnancy).

### **Costs**

There will be no cost to you to take part in the research study. The costs of your labor, delivery and care after delivery will be billed to you or your insurance company in the usual manner.

### **Compensation**

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid \$XX to compensate you for the time and travel associated with the research study.

### **Payment for Injury or Harm**

(THIS SECTION WILL BE CENTER SPECIFIC.) This hospital is not able to offer financial compensation or absorb the costs of medical treatment in the event of injury resulting from the research. In the event of such injury, treatment will be provided but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

### **Right to Withdraw From the Research Study**

This study is voluntary and it is up to you to decide whether or not you want to participate. You are free to withdraw your consent and stop taking part in this research study at any time without giving a reason. Refusal to take part or the decision to withdraw from the study will involve no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not affect your legal rights or quality of health care that you will receive at this hospital. Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

### **Right of the Investigator to Withdraw**

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

### **Confidentiality**

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the nurse, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes whether you are married, whether you have a job, and type of medical insurance. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be held at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland) in a database consisting of information from all of the participants in this study. Your information in the database will **only** be used for statistical analysis and may appear in scientific publications but will not identify you. The information at the data coordinating center does **not** include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead the data center will use a unique code for each person consisting of a number and the first letter of your first name. The key to the code linking the data to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected. Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions asked by the representative of the board.
- The Office for Human Research Protections (OHRP)
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your or your baby's medical chart may also be sent to research investigators at one of the other enrolling centers or the data coordinating center for review. If your chart is sent, identifying information, such as name, address, social security number, or hospital number will be removed.

The results of this research study will be provided to the sponsor, NICHD, (and/or its representatives). In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data.

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

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. \_\_\_\_\_ of the \_\_\_\_\_ stating that you are canceling your authorization. This letter must be signed and dated and sent to this

address: \_\_\_\_\_. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this revocation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

### **Questions**

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research study.

If you have questions or are hurt while taking part in this research study, you should contact \_\_\_\_\_ at (\_\_\_\_) \_\_\_\_-\_\_\_\_.

If you have any questions about the informed consent process or any other rights as a research subject, please contact \_\_\_\_\_, at (\_\_\_\_) \_\_\_\_-\_\_\_\_. \_\_\_\_\_.

### **Signatures**

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

YES \_\_\_\_\_ I give permission to be contacted in the future for research purposes.

NO \_\_\_\_\_ I do not give permission to be contacted in the future for research purposes.

\_\_\_\_\_  
Participant  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Person Obtaining Consent  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**ASSENT FOR FEMALES UNDER 18 YEARS of AGE (if required by Center IRB):**

I agree \_\_\_\_\_ I do not agree \_\_\_\_\_ to participate in this study.

This has been explained to me by \_\_\_\_\_.

\_\_\_\_\_  
Signature of Minor

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name of Subject

\_\_\_\_\_  
Age

Please provide either one or both parental signatures as instructed by your IRB.

\_\_\_\_\_  
Signature of Mother/Guardian

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Father/Guardian

\_\_\_\_\_  
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' Name  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

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# Induction in Nulliparous Women at 39 Weeks to Prevent Adverse Outcomes: A Randomized Controlled Trial

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## Protocol

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### A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

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*Eunice Kennedy Shriver*

National Institute of Child Health and Human Development (NICHD)  
Maternal-Fetal Medicine Units (MFMU)  
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# 1 Introduction

## 1.1 Study Abstract

Recently, several retrospective studies have shown that certain maternal and perinatal complications increase with gestational age after 37-38 completed weeks. This has called into question whether it is appropriate to wait until 41 weeks for induction in uncomplicated pregnancies. Although it has traditionally been held that the disadvantage of labor induction is that it increases the risk of cesarean delivery, this conclusion is based on studies with methodological flaws. In these studies, women who were electively induced were compared by gestational week with those who labored spontaneously. This is not the most appropriate comparison group because women who are induced at 39 weeks, for example, would not otherwise have immediate spontaneous labor. Instead, the most fitting comparison group should be composed of women who are expectantly managed. The studies that have used this comparison group have largely failed to demonstrate the association between induction and cesarean delivery, as have the small trials where women were randomized to labor induction or expectant management. Thus, whether labor induction at 39 weeks of gestation modifies maternal and perinatal outcomes, compared with expectant management, remains unknown.

This protocol describes a randomized trial of 6000 women to assess whether a policy of elective induction of labor at 39 weeks of gestation compared with expectant management will improve outcomes.

## 1.2 Primary Hypothesis

Among nulliparous women with singleton uncomplicated term pregnancies, elective induction of labor at 39 weeks, compared with expectant management, reduces the risk of severe neonatal morbidity and perinatal mortality.

## 1.3 Purpose of the Study Protocol

This protocol describes the background, design and organization of the randomized clinical trial and may be viewed as a written agreement among the study investigators. The Data and Safety Monitoring Committee (DSMC) and the Network Advisory Board review the protocol. Before recruitment begins, the protocol is approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network Steering Committee, and the Institutional Review Board (IRB) of each clinical center. Any changes to the protocol during the study period require the approval of the Steering Committee and the IRBs; major changes also require the approval of the DSMC.

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

## 2 Background

### 2.1 Introduction

Post dates pregnancy, defined as a gestation that persists beyond 294 days or 42 weeks' gestation, is associated with an increased risk of perinatal morbidity and mortality.<sup>1</sup> Several studies have shown that as pregnancy extends beyond 42 weeks the risk of oligohydramnios, macrosomia, fetal birth injury, meconium aspiration syndrome, and stillbirth increase significantly.<sup>1</sup> To avoid these risks, common practice has been to induce labor once 42 weeks has been reached. Indeed, because these risks begin to increase even before 42 weeks, many investigators have suggested that a policy of induction of labor at 41 weeks can improve pregnancy outcomes. In 2006 a Cochrane review was conducted of all trials in which women were randomized to induction of labor at 41-42 weeks or expectant management with fetal surveillance (including the MFMU Network's trial). The investigators found that a policy of induction of labor at or beyond 41 completed weeks was associated with fewer (all-cause) perinatal deaths (RR 0.3 95% CI 0.09, 0.99), with no evidence of a statistically significant difference in the cesarean section rate for women in the induction group (RR 0.92 95% CI 0.76, 1.12).<sup>2</sup>

The American Congress of Obstetricians and Gynecologists states that both expectant management and labor induction at 41 weeks are associated with low complication rates and good perinatal outcomes in low-risk post term women but that there appears to be a small advantage to labor induction, regardless of parity or method of induction.<sup>1</sup> Recently, data have been published showing increased rates of complications beyond 39 weeks, suggesting that it may be advantageous to induce uncomplicated pregnancies at an earlier gestation than 41 weeks.<sup>3-15</sup>

### 2.2 Complications of Term Pregnancies beyond 39 Weeks of Gestation

#### 2.2.1 Maternal Complications

Several studies have demonstrated that certain maternal complications increase in a continuous fashion after 37-38 completed weeks.<sup>3-8</sup> Investigators have reported that pregnancies that continue beyond 39 weeks are associated with increased risks of cesarean section, operative vaginal delivery, 3<sup>rd</sup> and 4<sup>th</sup> degree lacerations, and chorioamnionitis.<sup>3-7,9</sup>

Table 1 summarizes the maternal data from the largest and most recent cohort studies that have examined adverse outcomes in term pregnancies. Most of these studies examined maternal complications in multivariable models and found that gestational age beyond 39 weeks was predictive of increased risk even when controlling for known confounders such as maternal age, ethnicity, education, parity, length of labor, induction, and birth weight.

Table 1. Maternal Complications in Singleton Gestation by Gestational Week

Population and Reference	39 weeks	40 weeks	41 weeks	Adjusted OR (95% CI) 41 wks vs 39 wks in a Multivariable Model
<b>Primary cesarean delivery (multiparas and nulliparas)</b>				
N=45,673; 1992-2002 <sup>4</sup>	14.0%	15.9%**	21.2%**	1.32 (1.17, 1.53)
N=32,828; low risk; 1976-2001 <sup>3</sup>	9.2%	10.4%**	14.1%**	1.44 (1.28, 1.62)
N=119,254; low risk; 1995-99 <sup>5</sup>	8.8%	9.0%	14.0%**	1.28 (1.20, 1.36)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	12.8%	14.1%**	19.8%**	1.46 (1.44, 1.48)
<b>Primary cesarean delivery rates by weeks' gestation in nulliparas only</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	11.4%	14.2%*	18.9%**	Not available
N=119,254; low risk; 1995-99 <sup>5</sup>	14.4%	14.9%	21.9%**	Not available
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	21.5%	23.3%**	30.1%**	Not available
<b>Operative vaginal delivery</b>				
N=45,673; 1992-2002 <sup>4</sup>	15.5%	17.9%**	18.5%	1.14 (1.05, 1.23)
N=32,828; low risk; 1976-2001 <sup>3</sup>	14.8%	16.4%**	17.4%**	1.22 (1.10, 1.44)
N=119,254; low risk; 1995-99 <sup>5</sup>	9.4%	10.9%**	13.3%**	1.29 (1.20, 1.36)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	7.6%	8.1%**	9.6%**	1.14 (1.11, 1.16)
<b>3<sup>rd</sup> and 4<sup>th</sup> degree lacerations</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	9.4%	10.8%**	12.0%**	1.26 (1.10, 1.44)
N=119,254; low risk; 1995-99 <sup>5</sup>	4.0%	4.6%*	6.7%**	1.58 (1.44, 1.73)
<b>Postpartum hemorrhage</b>				
N=32,828; low risk; 1976-2001 <sup>3</sup>	13.4%	12.8%	16.0%**	1.18 (1.06, 2.31)
N=119,254; low risk; 1995-99 <sup>5</sup>	2.5%	3.1%**	4.1%**	1.21 (1.10, 1.32)
<b>Febrile morbidity</b>				
N=45,673; 1992-2002 <sup>4</sup>	1.7%	2.3%	2.7%**	1.46 (1.14, 1.87)
N=32,828; low risk; 1976-2001 <sup>3</sup>	5.2%	6.0%**	7.7%**	1.28 (1.11, 1.49)
N=119,254; low risk; 1995-99 <sup>5</sup>	2.7%	3.7%**	5.1%**	1.46 (1.14, 1.87)
N=2,928,722; low risk; from US natality data 2003 <sup>7</sup>	1.6%	2.0%**	2.7%**	1.49 (1.45, 1.54)

Statistical significance compared with rate of outcome in the previous week gestation: \* p<.01, \*\* p<.001

## 2.2.2 Infant Outcomes

Studies have also demonstrated that the rates of adverse neonatal outcomes are increased in pregnancies that extend beyond 39 weeks.<sup>4,6</sup> In a study of singleton deliveries in Scotland between 1985 and 1996, Smith showed that the risk of perinatal death (stillbirth or neonatal death) nadirs at 39 weeks.<sup>8</sup> In a study of deliveries registered in an area of London, the rate of stillbirth increased progressively with advancing gestation from 37 to 43 weeks.<sup>10</sup> Abnormal neonatal acid-base status has been shown to increase in pregnancies delivered beyond 39 weeks.<sup>6,11</sup>

In a retrospective cohort study of singleton, cephalic, low-risk neonates delivered at term, Caughey et al. concluded that neonatal complications of term pregnancy increase in a continuous, rather than in a threshold fashion. In this cohort the incidence of severe neonatal complications was increased 1.5-2 fold in pregnancies delivered at 40-41 weeks compared with those delivered at 39 weeks (Table 2).<sup>6</sup> Other investigators reported similar trends in neonatal morbidity for pregnancies advancing beyond 39 weeks.<sup>7,11,12</sup>

**Table 2. Association of Gestational Age with Severe Neonatal Complications**

Gestational week	Percent with complications	Odds ratio (95% CI)
39 weeks	1.84%	referent
40 weeks	2.31%	1.47 (1.09, 1.98)
41 weeks	3.14%	2.04 (1.50, 2.78)
42 weeks	3.82%	2.37 (1.63, 3.49)

Based on Caughey et al 2005; severe neonatal complications defined as birth trauma, seizures, intracranial hemorrhage, sepsis, meconium aspiration syndrome, respiratory distress syndrome

In contrast with maternal outcomes, there is clear evidence that adverse neonatal outcomes are more common when elective delivery is undertaken at term but prior to 39 weeks. Several investigations demonstrated an increase in neonatal morbidity for infants delivered at 37-38 weeks, compared with those delivered at 39 weeks or beyond. Specifically, at ages before 39 weeks, the risk of NICU admission, RDS, mechanical ventilation, and hypoglycemia are increased, particularly for infants delivered by cesarean section.<sup>13-15</sup> While the risk of both stillbirth and infant death per 1000 ongoing pregnancies increases a modest amount between 37-39 weeks (0.7/1000 to 1.4/1000 respectively), the risk of more common adverse events (e.g., RDS, mechanical ventilation) is increased by a factor of 2 to 12.<sup>14,15</sup> Overall, elective delivery prior to 39 weeks is associated with an increase in respiratory and other adverse neonatal outcomes.

## 2.3 Results from MFMU Network Studies

Secondary analyses of NICHD MFMU Network data are consistent with the findings above for both maternal and neonatal outcomes. In the MFMU Network trial of fetal pulse oximetry (FOX), a secondary analysis of 4086 women found that the risks of a composite maternal outcome (treated uterine atony, blood transfusion, or peripartum infection) and cesarean delivery increased with increasing gestational age from 39 to 41 or more completed weeks (p value for trend < 0.001).<sup>16</sup>

In the Cesarean Registry, a composite outcome of death or adverse neonatal outcome increased from 8% to 11.3% as gestational age increased from 39 to 41 weeks in women undergoing elective repeat cesarean delivery.<sup>14</sup> Also, in the cohort of women in the FOX trial referenced above, risks of a similar composite adverse neonatal outcome increased with increasing gestational age after 39 weeks.<sup>16</sup>

In summary, available data lead to the hypothesis that planned delivery at 39 weeks will result in the fewest adverse maternal and perinatal outcomes.

## **2.4 Potential Risks and Benefits of Planned Elective Induction of Labor before 41 weeks**

If neonatal risks nadir at approximately 39 weeks, and if the risks of maternal and neonatal complications increase monotonically after 39 weeks, the question arises - do the risks of pregnancy prolongation beyond 39 weeks outweigh the risks of labor induction? Whereas planned cesarean delivery in the absence of medical or obstetric complications is performed at 39 completed weeks, planned induction of labor at 39 weeks has been discouraged due to a potential increase in risk of cesarean delivery. Indeed, several retrospective cohort studies indicate that induction of labor prior to 41 weeks is associated with an approximately 2-fold higher risk of cesarean in nulliparous women.<sup>17-22</sup> However, these studies have several important limitations.

First, a number of studies compared outcomes in women undergoing both indicated and elective inductions with those of spontaneously laboring women.<sup>20,23-26</sup> By including women with medical indications for induction (e.g., preeclampsia), it is possible that the higher rates of cesarean delivery observed in the induction group were due to the pregnancy complications and not the induction per se. Other studies have evaluated elective induction of labor separately.<sup>17,18,21,22,24,27,28</sup> They consistently showed that cesarean delivery is more common in those electively induced. However, in these studies, women who were electively induced were compared with those who were spontaneously laboring. While this is a convenient comparison group it is not the most appropriate one, because women who are induced at 39 weeks are not guaranteed the alternative of an immediate spontaneous labor. In other words, women and their providers cannot choose between elective induction and spontaneous labor, but between elective induction and expectant management. Expectant management at 39 weeks may result in a proximate spontaneous labor but also may result in circumstances (e.g., preeclampsia, need for labor induction at 42 weeks) that increase the risk of cesarean.<sup>29</sup> Therefore, the most fitting comparison group in an observational study of elective induction would be all women at 39 weeks with ongoing pregnancies.

One group of investigators performed an observational study with just such a nulliparous study population. Osmundson and colleagues compared outcomes of labor between nulliparous women who either underwent elective induction or expectant management at or beyond 39 weeks at a single center.<sup>30,31</sup> Moreover, these investigators ascertained cervical status of all women at 38-39 weeks, in order to remove the possibility of selection bias related to this factor. The findings of this study, in contrast with the prior studies that used spontaneously laboring comparison groups, revealed that elective induction at 39 weeks or greater, for either women with a favorable or unfavorable cervix, did not increase the cesarean delivery rate. Specifically, for nulliparas with a favorable cervix (modified Bishop score  $\geq 5$ ) the cesarean delivery rate was 21% in the electively induced group vs. 20% in the expectantly managed group ( $p = 0.84$ ). Similarly there was no significant difference in the cesarean rate for women with an unfavorable cervix (43% vs. 34%,  $p = .16$ ). This study calls into question the long-standing dogma that elective induction of labor prior to 41 weeks increases the frequency of cesarean delivery.

With regard to long-term outcomes of the offspring, there has not been consistent evidence that oxytocin use results in neurodevelopmental disorders.<sup>32-35</sup> Moreover, as with many studies about labor induction, the studies that have assessed associations between intrapartum oxytocin use and neurodevelopmental outcomes have had several fundamental methodological flaws. For example, women are often induced for indications which themselves may be associated with adverse neurodevelopmental outcomes; in such a case of “confounding by indication”, adequate adjustment for the confounding factors may be difficult if not impossible. There is not evidence that elective induction (i.e., an induction without an underlying medical or obstetric indication) specifically is associated with adverse long-term neurodevelopmental

outcomes. Moreover, these studies have typically evaluated women undergoing induction versus those undergoing spontaneous labor; this comparison is inappropriate and not clinically relevant,<sup>36</sup> as spontaneous labor is not a choice but an event. Indeed, many women who are not “induced” at a given gestational age will ultimately require induction or oxytocin augmentation at a later gestational age, or experience an obstetric complication which itself may be associated with a risk of adverse neurodevelopmental outcome, a risk that may have been prevented had the women been induced earlier. Thus, the clinically meaningful comparison is labor induction versus expectant management. Yet, there are no data that suggest that elective induction compared with expectant management increases the risk of neurodevelopmental disorders or other adverse long-term outcomes.

**Table 3. Randomized Controlled Trials of Elective Induction of Labor (EIOL) at 39-40 Weeks vs Expectant Management (EM)**

Year and Reference	N	Patient Population (% nullips)	Gestational Age at EIOL	Gestational Age for EM	Outcome: EIOL vs. EM (p>0.05 unless noted)
1975 <sup>37</sup>	228	• Multiparous or nulliparous (46%)	39-40 weeks	41 weeks	Cesarean: 4.5% vs 7.7%
1978 <sup>38</sup>	230	• Multiparous or nulliparous*	39 weeks	42 weeks	Cesarean: 4.3% vs 1% Operative vaginal delivery: 18.5% vs 20.7%
1979 <sup>39</sup>	112	• Multiparous or nulliparous (45%)** • Favorable cervix	40 weeks	42 weeks	Operative vaginal delivery: 2.3% vs 4.8%
1989 <sup>40</sup>	345	• Multiparous or nulliparous (54%) • Favorable cervix	40 weeks	42 weeks	Nulliparas: Cesarean: 1.0% vs 3.4% Operative vaginal delivery: 3.0% vs 3.4% Multiparas: Cesarean: 1.2% vs 0% Operative vaginal delivery: 1.2% vs 0%
1999 <sup>40</sup>	194	• Nulliparous <sup>†</sup>	39 weeks	42 weeks	Cesarean: 6.4% vs 5.6% Operative vaginal delivery: 53.4% vs 33.3% (p=.03)
2005 <sup>41</sup>	226	• Multiparous or nulliparous (45%) • Favorable cervix	39-40 weeks	42 weeks	Nulliparas: Cesarean: 13.3% vs 10.3% Multiparas: Cesarean: 2.8% vs 3.8%

\* Excluded women in EIOL group who had spontaneous labor before 39 weeks and women in EM group if failed to go into spontaneous labor by 42 weeks

\*\* Excluded women in either group with spontaneous labor before 40 weeks or who required a cesarean

† Excluded women in EIOL group who had spontaneous labor before 39 weeks and women in EM group if induced before 42 weeks or failed to go into spontaneous labor by 42 weeks

#### 2.4.1 Randomized Trials of Elective Induction at Term versus Expectant Management

There have been several small randomized clinical trials comparing elective induction of labor at 37-40 weeks' gestation with expectant management until 41-42 weeks (Table 3).<sup>37-42</sup> None of these studies found an increased frequency of cesarean section among induced participants. However, these trials have significant limitations. First, all were underpowered to detect the magnitude of increase in cesarean rate that would be considered clinically relevant. In addition, because two trials only included women with a favorable Bishop score, the generalizability of the data to women with an unfavorable score is limited.



Nevertheless, meta-analysis of these data generated by randomized trials reveals a reduction in the frequency of cesarean section with induction (RR 0.89; 95% CI 0.81 to 0.97).<sup>2</sup> Although it did not address elective induction, the Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT), a randomized trial comparing induction to expectant management for women with hypertensive disease of pregnancy, also demonstrates that labor induction may not increase the risk of cesarean (14% in the induction of labor group versus 19% in the expectant management group (RR 0.75; 95% CI 0.55-1.04).<sup>43</sup>

## **2.5 Rationale for a Randomized Clinical Trial**

Given the reported increased risks of adverse events in pregnancies extending beyond 39 weeks it has been hypothesized that a policy of planned elective induction at 39 weeks could improve outcomes for the infant and the mother. For multiparous patients, especially those with a favorable cervix, it is perhaps easy to justify an elective induction at 39 weeks given the low risk of cesarean section. However, for nulliparous patients the current evidence, derived mainly from retrospective observational studies, does not allow a clear recommendation. Nevertheless, a trend towards an increased rate of elective labor induction in pregnancies at 39 weeks has been reported, indicating that practitioners are more commonly using elective induction at this gestational age,<sup>43</sup> even as others caution against routine elective induction prior to 41 weeks given the reported increased risk of cesarean delivery.<sup>19,44,45,46</sup> Ultimately, a randomized controlled trial is necessary to satisfactorily understand whether elective induction of labor of nulliparas at 39 weeks improves neonatal and maternal outcomes.

## 3 Study Design

### 3.1 Primary Research Question

This randomized trial will address the primary research question: does elective induction of labor in nulliparous women at 39 weeks improve perinatal outcome compared with expectant management?

### 3.2 Secondary Research Questions

Secondary research questions this study will address are:

- Does elective induction of labor in nulliparous women at 39 weeks reduce the risk of any of the maternal outcomes listed in Section 4.7.2?
- Does elective induction of labor in nulliparous women at 39 weeks reduce the risk of any of the fetal and neonatal outcomes listed in section 4.7.3?
- Does elective induction of labor in nulliparous women at 39 weeks modify the utilization of the medical resources listed in section 4.7.4?
- If the two groups show a difference in the incidence of the primary outcome or cesarean, does the proposed effect of elective induction of labor in nulliparous women at 39 weeks vary according to any of the subgroups listed in section 5.5?

### 3.3 Design Summary

The study is a randomized controlled multi-center clinical trial of 6000 women at 38 weeks 0 days to 38 weeks 6 days randomized to one of two arms at participating MFMU Network clinical centers.

- Elective induction of labor between 39 weeks 0 days and 39 weeks 4 days
- Expectant management (unless a medical indication arises) until at least 40 weeks 5 days.

### 3.4 Eligibility Criteria

#### 3.4.1 Inclusion Criteria

1. Nulliparous - no previous pregnancy beyond 20 weeks
2. Singleton gestation. Twin gestation reduced to singleton, either spontaneously or therapeutically, is not eligible unless the reduction occurred before 14 weeks project gestational age (see below).
3. Gestational age at randomization between 38 weeks 0 days and 38 weeks 6 days inclusive based on clinical information and evaluation of the earliest ultrasound as described in Gestational Age Determination in Section 3.4.2 below.

#### 3.4.2 Gestational Age Determination

Gestational age is determined using criteria proposed by the American Congress of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine and the Society for Maternal-Fetal Medicine<sup>47</sup> and is denoted “project gestational age”. The “project EDC”, which is based on the project gestational age, cannot be revised once a determination has been made. If the pregnancy is conceived by in-vitro fertilization, project gestational age is calculated from the date of embryo transfer and the embryo age at transfer. If the pregnancy is conceived spontaneously (including ovulation induction and artificial

insemination) information from the earliest dating ultrasound and the last menstrual period are used to determine project gestational age. The following algorithm is used:

- The first day of the last menstrual period (LMP) is determined, and a judgment made as to whether or not the patient has a “sure” LMP date.
- If the LMP date is unsure, measurement(s) obtained at the patient’s first dating ultrasound examination is used to determine the project gestational age. The first dating ultrasound must have been conducted before 14 weeks 0 days by crown rump length (CRL).
- If the LMP date is sure, project gestational age is determined by a comparison between the gestational age by LMP and by the earliest dating ultrasound. The first dating ultrasound must have been conducted before 21 weeks 0 days by LMP. If the ultrasound confirms the gestational age by LMP as in the table below, the LMP-derived gestational age is used to determine the project gestational age. Otherwise, project gestational age will be determined based upon the ultrasound measurement.

**Table 4. Cutoffs for Using LMP to Determine Gestational Age for Sure LMP**

Gestational age at first ultrasound by LMP	Ultrasound method of measurement	Ultrasound agreement with LMP
Up to 8 weeks 6 days	CRL	± 5 days
9 weeks 0 days to 13 weeks 6 days	CRL	± 7 days
14 weeks 0 days to 15 weeks 6 days	Per institution	± 7 days
16 weeks 0 days to 20 weeks 6 days	Per institution	± 10 days

### 3.4.3 Exclusion Criteria

1. Project gestational age at date of first ultrasound is > 20 weeks 6 days
2. Plan for induction of labor prior to 40 weeks 5 days
3. Plan for cesarean delivery or contraindication to labor
4. Breech presentation
5. Signs of labor (regular painful contractions with cervical change)
6. Fetal demise or known major fetal anomaly
7. Heparin or low-molecular weight heparin during the current pregnancy
8. Placenta previa, accreta, vasa previa
9. Active vaginal bleeding greater than bloody show
10. Ruptured membranes
11. Cerclage in current pregnancy
12. Known oligohydramnios, defined as AFI < 5 or MVP < 2
13. Fetal growth restriction, defined as EFW < 10<sup>th</sup> percentile
14. Known HIV positivity because of modified delivery plan

15. Major maternal medical illness associated with increased risk for adverse pregnancy outcome (for example, any diabetes mellitus, lupus, any hypertensive disorder, cardiac disease, renal insufficiency)
16. Refusal of blood products
17. Participation in another interventional study that influences management of labor at delivery or perinatal morbidity or mortality
18. Delivery planned elsewhere at a non-Network site

### **3.5 Informed Consent Criteria**

Each center will develop its own consent forms according to the requirements of its own institutional review board using the model consent form in Appendix B. Each center will also develop its own patient research authorization documents, as required by the HIPAA Privacy Rule, following the guidelines of its own institution. A copy of the signed consent form will be provided to the patient.

Women who are not fluent in English will be enrolled by a person fluent in their language. Both verbal and written informed consent and authorization will be obtained in that language; if this is not possible the patient will be excluded.

### **3.6 Randomization Method**

Randomization for consenting women will occur at 38 weeks 0 days to 38 weeks 6 days of gestation. Consenting women will be assigned to induction of labor at 39 weeks 0 days to 39 weeks 4 days or expectant management in a 1:1 ratio according to a randomization sequence prepared and maintained centrally by the Biostatistical Coordinating Center (BCC).

The simple urn method will be used to generate the randomization sequences because it provides a high probability of balance in treatment assignments, it is unpredictable, and it allows an explicit randomization analysis to be conducted with relative ease.<sup>48</sup> Randomization will be stratified by clinical site to assure balance between the two treatment groups with respect to anticipated differences in the clinic populations and possible differences in patient management.

## 4 Study Procedures

### 4.1 Screening for Eligibility and Consent

All nulliparous women with a singleton gestation between 34 and 38 weeks are potentially eligible for screening. Inclusion/exclusion criteria will be reviewed with the patient's chart.

If a patient appears to meet the criteria for the trial, she will be told about the study and asked for written informed consent to participate in the trial. Consent may be obtained anytime from 34 weeks 0 days to 38 weeks 6 days of gestation.

Each patient must undergo a digital cervical exam between 72 hours prior to randomization and 24 hours after randomization. The three components of the modified Bishop score must be obtained during this exam. Table 5 provides the scoring system that uses the following three components to derive the modified Bishop score:

- Cervical dilation
- Cervical length or effacement
- Fetal station

**Table 5. Scoring System for the Modified Bishop Score**

Station (in relation to the spines)	-3 cm	-2 cm	-1 - 0 cm	1 - 2 cm
	0	1	2	3
Dilation (of the cervix)	0 cm	1-2 cm	3-4 cm	>4 cm
	0	2	4	6
Length (of the cervix)	3 cm	2 cm	1 cm	0 cm
	0	1	2	3

### 4.2 Randomization

Eligibility should be verified again before randomization. Eligible and consenting patients will be randomized by certified research staff using an internet based randomization system maintained by the BCC. Randomization will occur when the patient is from 38 weeks 0 days to 38 weeks 6 days of gestation. The patient will be assigned either to the induction of labor group or the expectant management group.

If the patient has had a digital cervical exam within the past 72 hours, and all components of the modified Bishop score are documented (cervical dilation, cervical effacement or cervical length, and fetal station), randomization may be done in person or over the telephone. If the patient has not had a digital cervical exam within the past 72 hours, or if components of the modified Bishop score are not documented, she must be randomized in person and have a digital cervical exam within that same day.

### **4.3 Baseline Procedures**

In addition to information collected for eligibility, project gestational age, and project EDC determination, the following information will be obtained at randomization from a patient interview followed by a review of her chart:

- Components of the modified Bishop score: cervical dilation, cervical length or effacement, and fetal station from digital cervical exam
- Demographic information: age, race, ethnicity, insurance status
- Medical history: first clinic weight, current weight, height, chronic disease history
- Obstetrical history including outcome(s) of any prior pregnancies
- Social history: marital status, alcohol use, and tobacco use
- Current pregnancy complications

### **4.4 Study Procedures**

Women randomized to induction of labor will undergo induction via oxytocin at 39 weeks 0 days to 39 weeks 4 days. Those with an unfavorable cervix (modified Bishop score < 5) will first undergo cervical ripening (method left to the discretion of the patient's physician) in conjunction with or followed by oxytocin stimulation unless a contraindication arises.

Women randomized to expectant management will have at least weekly follow-up visits with their providers and, unless a medical indication is present, will continue pregnancy until at least 40 weeks 5 days of gestation. Antepartum fetal testing will be initiated no later than 41 weeks 6 days according to policies at each center. All patients will undergo induction via oxytocin by 42 weeks 2 days.

### **4.5 Patient Management and Follow-up**

Patients in the induction of labor group (as well as patients in the expectant management group that undergo induction of labor) should be allowed adequate time to labor before considering the induction "failed" and proceeding to cesarean section. An induction will be considered "failed" if at least 12 hours have elapsed since both rupture of membranes and use of a uterine stimulant and the patient remains in latent labor. It is expected that the fetal heart rate will be monitored while the patient is being induced (including ripening) and during labor and that patients will stay in the hospital until delivery once the induction (including ripening) is started. Mechanical ripening using a Foley catheter without saline infusion is permitted without monitoring and may be used in an outpatient setting according to policies at each center.

For patients in the expectant management group, only a valid medical indication should warrant delivery before 40 weeks and 5 days. Otherwise, no attempt will be made to alter or mandate clinical management of the subjects.

Women will be asked about pain experienced during childbirth and asked to complete a questionnaire on feelings of control during childbirth. All women will be contacted at six weeks postpartum to determine unanticipated outpatient or inpatient visits for them or their infants since discharge and to complete the same questionnaire about feelings of control again.

## **4.6 Adverse Event Reporting**

Detailed information concerning adverse events will be collected and evaluated throughout the conduct of the protocol.

The NICHD Project Scientist and the BCC will be notified within seventy-two hours of any maternal death, perinatal death, or life-threatening maternal event by email/phone/fax, if the event occurred in a MFMU Network hospital. For any maternal death, perinatal death, or life-threatening maternal event occurring outside a MFMU Network hospital, the adverse event must be reported to the NICHD and the BCC within twenty-four hours of being notified. These and other adverse events deemed serious, unexpected and definitely, possibly or probably related, will be immediately (within twenty-four hours of notification) forwarded by the BCC to the DSMC Chair, NIH representative, and any other DSMC member who requests notification. If a death is reported, a copy of the patient's medical record will be made.

Adverse events which do not qualify under the above definition must be reported to the BCC within 7 days of being notified. These adverse events will be collected and sent to the Chair, NIH representative, and any other requesting DSMC member on a monthly basis. The Chair decides whether the adverse event reports should be disseminated to the rest of the committee, and whether a follow-up call or meeting is required. NICHD representatives may also request follow-up of specific events. All adverse events will be considered along with other interim safety data in the DSMC deliberations.

## **4.7 Study Outcome Measures and Ascertainment**

### **4.7.1 Primary Outcome**

The primary outcome is a composite of severe neonatal morbidity and perinatal mortality (any one of the following):

- Antepartum, intrapartum, or neonatal death
- Intubation, continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for ventilation or cardiopulmonary resuscitation within first 72 hours
- Apgar  $\leq 3$  at 5 minutes
- Neonatal encephalopathy as defined by Shankaran et al.<sup>49</sup>
- Seizures
- Sepsis. The diagnosis of sepsis will require the presence of a clinically ill infant in whom systemic infection is suspected with a positive blood, CSF, or catheterized/suprapubic urine culture; or, in the absence of positive cultures, clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection.
- Pneumonia confirmed by X-ray or positive blood culture.
- Meconium aspiration syndrome
- Birth trauma (bone fractures, brachial plexus palsy, other neurologic injury, retinal hemorrhage, or facial nerve palsy)
- Intracranial hemorrhage (intraventricular hemorrhage grades III and IV, subgaleal hematoma, subdural hematoma, or subarachnoid hematoma)
- Hypotension requiring pressor support

#### **4.7.2 Maternal Secondary Outcomes**

1. Cesarean delivery and indication
2. Incisional extensions at cesarean section, including J shape or T shape; or cervical traumas
3. Operative vaginal delivery and indication
4. Chorioamnionitis, defined as a clinical diagnosis before delivery
5. Third or fourth degree perineal laceration
6. Maternal death
7. Admission to intensive care unit (ICU)
8. Preeclampsia/gestational hypertension
9. Postpartum hemorrhage, defined as any of the following:
  - Transfusion
  - Non-elective hysterectomy
  - Use of two or more uterotonics other than oxytocin
  - Other surgical interventions such as uterine compression sutures, uterine artery ligation, embolization, hypogastric ligation, or balloon tamponade
  - Curettage
10. Interval from randomization to delivery
11. Gestational age at delivery
12. Maternal postpartum infection, defined as any of the following:
  - Clinical diagnosis of endometritis
  - Wound reopened for hematoma, seroma, infection or other reasons
  - Cellulitis requiring antibiotics
  - Pneumonia
  - Pyelonephritis
  - Bacteremia unknown source
  - Septic pelvic thrombosis
13. Maternal venous thromboembolism (deep venous thrombosis or pulmonary embolism)

#### **4.7.3 Fetal and Neonatal Secondary Outcomes**

1. Birth weight
2. Duration of respiratory support including ventilator, CPAP, high-flow nasal cannula (HFNC)
3. Cephalohematoma
4. Shoulder dystocia
5. Transfusion of blood products or blood
6. Hyperbilirubinemia requiring phototherapy or exchange transfusion



7. Hypoglycemia (glucose < 35 mg/dl) requiring IV therapy
8. Admission to neonatal intensive care unit (NICU) or intermediate care unit

#### **4.7.4 Utilization of Medical Resources**

1. Number of hours on the labor and delivery unit
2. Maternal postpartum length of hospital stay
3. Neonatal length of hospital stay

## 5 Statistical Considerations

### 5.1 Data Relevant to the Primary Outcome

To estimate the rate of the primary outcome in the expectant management group, data from the MFMU Network's APEX study were evaluated. APEX was an observational study of approximately one-third of all deliveries at 25 hospitals in the MFMU Network, collected over a three-year period. For this analysis only nulliparous women with a singleton pregnancy delivered at 39 weeks 0 days to 42 weeks 0 days were included; those with diabetes, hypertension before 38 weeks, previa and abruption were excluded, yielding a cohort of 24,683 women. A composite outcome as close as possible to the proposed composite primary outcome for this trial was evaluated in these women. However, APEX only included pregnancies with fetal heart tones on admission for delivery and therefore stillbirth would be slightly underestimated. In addition, presence of thick meconium was used as a surrogate for meconium aspiration syndrome. The outcome rate in this cohort was 2.3% excluding presence of thick meconium; with thick meconium present the outcome rate was 9.3%. The real primary outcome rate could be expected to be between these two estimates.

Also, among women in the FOX trial, risks of adverse neonatal outcome at term (neonatal composite outcome including death, respiratory distress, seizure, sepsis, intubation and ventilator support, 5 minute Apgar score of 3 or less or hypoxic ischemic encephalopathy) were 3.7% at 36-38 weeks, 3.5% at 39 weeks, 3.8% at 40 weeks and 5.0% at  $\geq 41$  weeks.<sup>38</sup>

Therefore the neonatal composite outcome rate for pregnancies expectantly managed beyond 39 weeks would be expected to be between 3.5% and 5%. This is consistent with other literature presented in Chapter 1.

### 5.2 Sample Size and Power

#### 5.2.1 Primary Outcome

Table 6 shows the sample sizes per group (rounded up to the next 10) to detect a 35-40% reduction in the primary outcome, with 80% to 90% power, assuming type I error of 5% 2-sided and primary outcome rate in the expectant management arm between 3.5% and 5%. Some women will labor after randomization but prior to when their randomized assignment could be implemented (i.e., before 39 weeks). In addition, some women may undergo an elective induction off-protocol before 40 weeks, 5 days without a specific indication. These 'crossovers' would therefore behave more like the elective induction group; and it is assumed that their primary outcome rate would be the same as that of the elective induction group. This has the effect of reducing the effect size slightly depending on the proportion of crossovers: for example with 5% crossovers, the 40% nominal reduction becomes 39%.

Sample sizes were adjusted to take into account that between 5 and 10% of the women in the expectant management group will behave more like the elective induction group. The actual effect sizes are shown in parentheses in the table.

Data from observational studies suggest that a policy of induction of labor at 39 weeks may result in an equivalent reduction in adverse outcome.<sup>6, 46</sup> Using a type I error of 5% 2-sided and power of 85%, and an estimate that 7.5% of women in the expectant management group will be crossovers, 3000 women in each group (total N= 6000) would be needed to detect the actual reduction in primary outcome of 38%.

If the primary outcome rate is as high as 5%, a sample size of 6000 patients is sufficient to detect a 33-34% reduction in the primary outcome with at least 85% power, again assuming that 7.5% of women will be crossovers.

**Table 6. Sample Sizes per Group for Different Primary Outcome Rates, Power and Effect Sizes**

Reduction in Primary Outcome Rate (Reduction Adjusted for Crossover)	Power %	Nominal Primary Outcome Rate in Expectant Management Group			
		3.5%	4.0%	4.5%	5.0%
0% Crossover					
35% (35%)	80	3030	2650	2350	2120
	85	3460	3030	2690	2420
	90	4050	3540	3150	2840
40% (40%)	80	2250	1970	1750	1570
	85	2570	2250	2000	1800
	90	3010	2630	2340	2110
5% Crossover					
35% (33.8%)	80	3320	2900	2580	2320
	85	3790	3320	2950	2660
	90	4440	3880	3450	3110
40% (38.8%)	80	2460	2150	1910	1720
	85	2810	2460	2190	1970
	90	3290	2880	2560	2300
7.5% Crossover					
35% (33.2%)	80	3480	3040	2710	2440
	85	3980	3480	3100	2790
	90	4660	4070	3620	3260
40% (38.1%)	80	2580	2260	2010	1810
	85	2950	2580	2290	2060
	90	3450	3020	2680	2420
10% Crossover					
35% (32.6%)	80	3650	3200	2840	2560
	85	4180	3660	3250	2930
	90	4890	4280	3810	3430
40% (37.5%)	80	2700	2370	2100	1890
	85	3090	2710	2410	2170
	90	3620	3170	2820	2530

### 5.2.2 Cesarean Delivery

Assuming that the rate of cesarean delivery is 30% in the expectant management group, a sample size of 6000 women also yields more than 90% power to detect a nominal 15% increase or decrease even after adjusting for 7.5% crossovers.

### **5.3 Feasibility**

Given that the sample size estimates are based on a composite of rare outcomes, it is planned that the primary outcome rate in the expectant management group be examined in the first 1000 patients. These data would be presented to the DSMC before any comparison by group, and the committee would be charged with making a recommendation regarding potential revision of the sample size in addition to addressing the feasibility of answering the primary research question.

### **5.4 Interim Analysis**

The Data and Safety Monitoring Committee (DSMC) meets in person at least once per year and more often if recommended by the committee. Before each of the annual meetings, a formal detailed report will be written by the Biostatistical Coordinating Center (BCC) which presents all baseline variables, protocol adherence, side effects, all adverse events reported, as well as center performance in terms of recruitment, data quality, loss to follow-up and protocol violations.

Once sufficient patients have been accrued into the trial, the report will also include a formal interim analysis evaluating the primary outcome by treatment group. For this evaluation, a cohort of patients is chosen consisting of all patients randomized before a certain date so that the analysis cohort does not depend on gestational age at delivery.

The main statistical issue relevant to interim analysis is the problem of performing multiple tests of significance on accumulating data. For this trial, the group sequential method of Lan and DeMets will be used to characterize the rate at which the type I error is spent.<sup>50</sup> This method is flexible with regard to the timing of the interim analyses. Asymmetric stopping boundaries will be used for the Lan-deMets procedure. The upper boundary which describes the stopping rule for benefit will be based on 1-sided type I error of .025 and the Lan-deMets generalization of the O'Brien-Fleming boundary.

The lower boundary will be based on a less stringent stopping rule: 1-sided type I error of .05 and the Lan-deMets generalization of the Pocock type boundary.

It is often useful to calculate conditional power given the observed data to date, and conditional on the future data showing the originally assumed design effect. If this conditional power is low (under 10 percent) the DSMC may consider termination for futility if the accrual rate is slow, with confidence that the Type II error is not greatly inflated.<sup>51</sup>

It is recognized that any decision to terminate the study would not be reached solely on statistical grounds but on a number of complex clinical and statistical considerations.

### **5.5 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, all relevant data available from each patient will be employed in the analyses. Patients will be included in the treatment group to which they were randomly assigned regardless of compliance.

The primary analysis will consist of a simple comparison of binomial proportions. The relative risk and confidence interval will be reported. The individual components of the composite outcome will also be examined. If the treatment groups are found to differ on a pre-treatment factor known to be a risk factor for the outcome, the statistical analysis will adjust for these differences. An evaluation of treatment by center interaction will be included. An analysis adjusting by center also will be performed to ensure that center differences do not change the conclusion.

If the two groups show a difference in the incidence of the primary outcome or cesarean, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout

particular subgroups of patients. Indeed, NIH guidelines require investigators to evaluate consistency between the genders and across racial subgroups (see Section 5.5.1). It should be noted, however, that subgroup analyses have been greatly abused, particularly when there is no overall treatment difference.<sup>52</sup> There is a strong temptation to search for a specific subpopulation in which the therapy is nevertheless effective. Yusuf et al. concluded “*the overall ‘average’ result of a randomized clinical trial is usually a more reliable estimate of the treatment effect in the various subgroups examined than are the observed effects in individual subgroups.*”<sup>53</sup> Thus subgroup analyses will be interpreted with care.

It is generally acknowledged that subgroup analysis that is pre-specified in the protocol has more validity than ad-hoc comparisons. The following factors will be considered for subgroup analysis, if there is a significant interaction between the factor of interest and the treatment effect.

- Race/ethnicity (see below)
- Modified Bishop score ( $< 5$  and  $\geq 5$ )
- Body mass index (obese and non-obese)
- Maternal age ( $< 35$  and  $\geq 35$  years)
- Admitting provider specialty (see below)

Loss to follow-up will be defined as no information regarding stillbirth or neonatal outcome. There should be a low loss to follow-up rate. It is possible that a woman would deliver at a non-Network hospital; however, a record release will be obtained at enrollment to ensure that delivery and neonatal information can be obtained. However, to determine whether the results are robust, a sensitivity analysis will be performed including patients lost to follow up with different assumptions regarding their outcome.

Since many of the secondary endpoints are dichotomous variables like the primary outcome, standard statistical methods for rates and proportions will be appropriate. The Wilcoxon rank sum test will be used to compare continuous variables, and survival analysis methodology may be used to compare time-to-event variables.

In general, analyses of data will be conducted to address the primary and secondary research questions of the trial, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study.

### **5.5.1 Racial/Ethnic Subgroup Analysis**

The racial/ethnic composition of patients of women recruited into the MFMU Network trials varies. Assuming for this trial that the composition is 25% African-American and 30% Hispanic, similar to the ongoing STAN trial, there is limited power (40-50%) to detect a 50% reduction in the primary outcome or cesarean in the separate subgroups.

### **5.5.2 Admitting Provider Specialty Subgroup Analysis**

Although admitting provider specialty is not a baseline variable, this variable will be evaluated for subgroup analysis if the two groups show a difference in the incidence of the primary outcome or cesarean, and if the test for interaction is significant. Elective induction of labor may be perceived as an intervention more likely utilized by obstetricians than by midwives, therefore it is important to demonstrate whether a treatment effect is present among patients treated by obstetricians and among patients treated by midwives.

## 6 Data Collection

### 6.1 Data Collection Forms

Data will be collected on standardized forms on which nearly all responses have been pre-coded. Each form is briefly described below:

- AR01 Screening Log.
- AR02 Eligibility and Randomization Form is completed for all patients eligible and consenting for the study, and documents the project gestational age and randomization digital cervical exam.
- AR04 Baseline Form is completed for all randomized patients. This form includes detailed demographic and social data, and medical and obstetrical history.
- AR05 Clinic and Hospital Visit Log documents scheduled and unscheduled clinic, urgent care and hospital visits, procedures and diagnostic tests, including the antepartum portion of the delivery admission.
- AR08 Labor and Delivery Summary Form documents specific pregnancy complications since randomization, in addition to labor, delivery and postpartum information.
- AR08A Labour Agency Questionnaire
- AR09 Neonatal Baseline Form records date and time of birth, delivery data and status at delivery, for each fetus/infant.
- AR10 Neonatal Outcome Form records outcome data for all infants admitted to the NICU or special care nursery.
- AR11 Patient Status Form documents loss to follow up/withdrawal status, last date of contact for lost to follow-up patients.
- AR12 Adverse Event Form records serious and non-serious adverse events.
- AR13 Postpartum Follow-up Form
- AR13A Maternal Follow-up Log documents the reasons and diagnoses associated with maternal clinic, urgent care and hospital visits
- AR13B Infant Follow-up Log documents the reasons and diagnoses associated with infant clinic, urgent care and hospital visits

### 6.2 Web Data Entry System

For this protocol, web data entry screens corresponding to the study forms listed above will be developed and maintained by the staff of the BCC. Clinical center staff will enter data into the MySQL database located at the BCC through a web data management system (MIDAS). The data are edited on-line for missing, out of range and inconsistent values. A Users' Manual documenting this system is provided to the centers by the BCC.

### 6.3 Centralized Data Management System

Daily data conversions from the MySQL database create up-to-date SAS datasets. Data are reviewed weekly using edit routines similar to those implemented on-line during data entry, as well as additional checks for data consistency within or across forms. A database of resulting potential data problems is

generated in MIDAS for initial review by BCC staff, who then evaluate the comments keyed in association with edits on missing or unusual values. Valid edits will be flagged in MIDAS for resolution at the clinical centers.

At regular intervals, specialized data reviews comparing data availability and consistency across forms are run by the BCC staff on the entire database or on a specific subset of data. These reports are also submitted to the centers for correction or clarification.

An audit trail, consisting of all prior versions of each data form as entered in the computer for each patient, is maintained so that the succession of corrections can be monitored.

#### **6.4 Performance Monitoring**

The BCC will present regular reports to the ARRIVE Subcommittee, the Steering Committee, and the Data and Safety Monitoring Committee. These include:

- Monthly Recruitment Reports - reports of the number of women screened and enrolled by month and by clinical center are provided monthly to the ARRIVE Subcommittee and all other members of the Steering Committee. Weekly or bi-weekly reports are provided electronically if needed.
- Quarterly Steering Committee Reports - reports detailing recruitment, baseline patient characteristics, data quality, incidence of missing data and adherence to study protocol by clinical center, are provided quarterly to the ARRIVE Subcommittee and all other members of the Steering Committee.
- Data and Safety Monitoring Committee Reports - 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 safety and efficacy data). The reports also include adverse events, loss to follow-up and all outcome variables as described previously in this protocol.

## 7 Study Administration

### 7.1 Organization and Funding

The study is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The study is conducted by the NICHD Maternal-Fetal Medicine Units (MFMU) Network, consisting of fourteen clinical centers, the Biostatistical Coordinating Center (BCC) and the NICHD, and is administered under cooperative agreements between each of the centers and the NICHD. Each of the funded institutions is represented by a Principal Investigator. A complete description of the organization of the MFMU Network is provided in the MFMU Network Policy Manual.

#### 7.1.1 Participating Clinical Centers

The participating Principal Investigators of the clinical 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 Biostatistical Coordinating Center

The BCC is responsible for all aspects of biostatistical design, data management, interim and final statistical analyses, and preparation of publications based on the study results. The Principal Investigator of the BCC 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 protocols, administration and conduct of the studies and preparation of publications.

#### 7.1.4 Network Advisory Board

Appointed by the NICHD, the members of the Network Advisory Board consist of a group of experts who are not affiliated with research being conducted by the Network and represent the disciplines of maternal-fetal medicine, neonatology and biostatistics/epidemiology. The role of the board includes the review and prioritization of proposed studies, in addition to the identification of scientifically and clinically important questions and ideas that might be conducted by the Network. The NICHD Project Scientist convenes and attends the meetings.

### 7.2 Committees

#### 7.2.1 Steering Committee

This committee consists of seventeen members. The Principal Investigator from each of the fourteen clinical centers, the BCC, and the NICHD MFMU Network Project Scientist are all voting members. The Chair of the Steering Committee may vote to break a tie. The Chair, a person independent of the participating institutions, is appointed by NICHD. The Steering Committee has the responsibility for identifying topics for Network studies, designing and conducting study protocols and monitoring study implementation, recruitment and protocol adherence. The committee receives recommendations from the Data and Safety Monitoring Committee and the Network Advisory Board.

#### 7.2.2 Protocol Subcommittee

The subcommittee consists of a chair (who is an investigator from one of the clinical centers), investigators from one or more other clinical centers, BCC staff, nurse coordinators, outside consultants



(if appropriate), and the NICHD Network Project Scientist. The Protocol Subcommittee is responsible for the preparation and conduct of the study, and reporting the progress of the study to the Steering Committee.

### **7.2.3 Publications Committee**

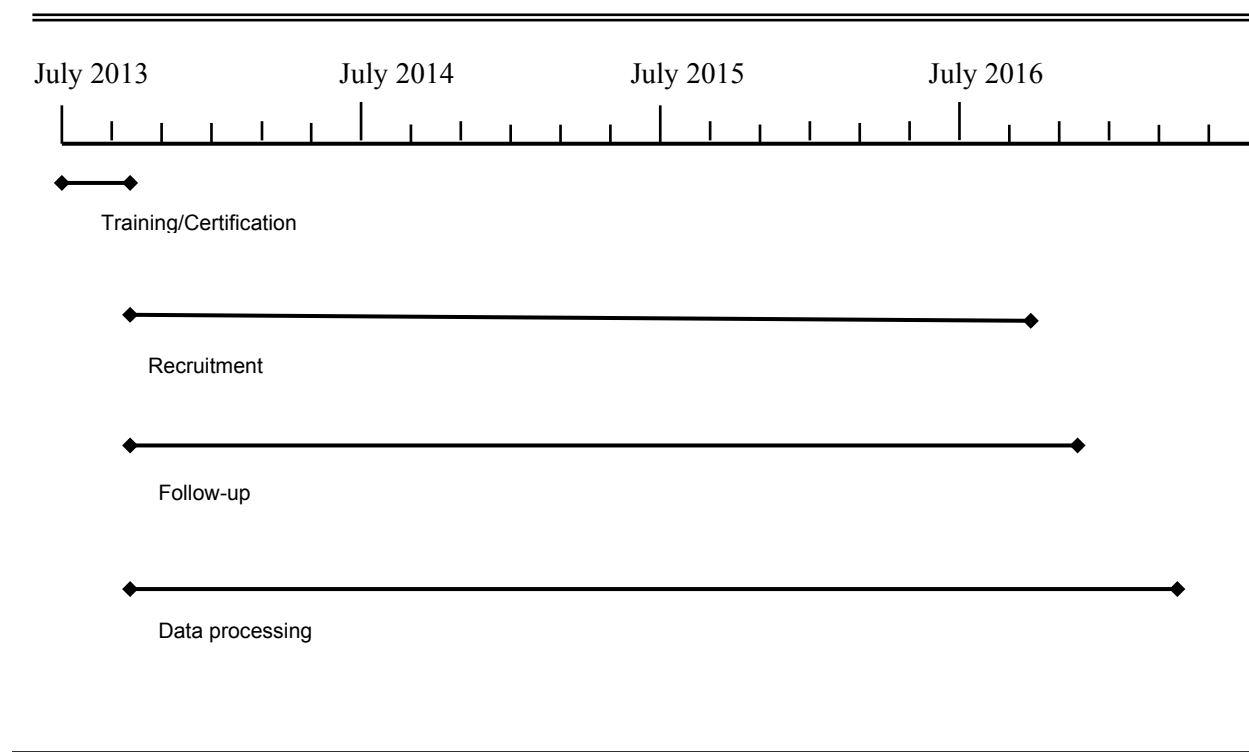
The Publications Committee is a standing committee of the Steering Committee. The functions of this committee are to develop publication policies and to review all manuscripts and abstracts prior to submission. The goals of this committee are fair and appropriate authorship credit and high quality publications.

### **7.2.4 Data and Safety Monitoring Committee**

The Data and Safety Monitoring Committee (DSMC), a group of individuals not affiliated with any of the participating institutions, was established by the NICHD. Before the trial can begin, the protocol must be approved by the committee. During the conduct of the study, the committee is charged with monitoring the emerging results for efficacy and safety, in addition to center performance and protocol adherence. Recommendations by the committee can include protocol modification, early termination for efficacy, or for unexpected safety problems. Recommendations are made to the NICHD and disseminated to the Steering Committee.

## 8 Study Timetable

Figure 1. Timetable



### 8.1 Training and Certification

During the study start-up period, preparation of the final case report forms, manual of operations, and randomization sequence, in addition to implementation of the data entry and management system will take place. Training will be held with the nurse coordinators in July and October 2013, with a projected study start date of October 2013. Each participating center must be certified to start the trial before recruitment at that center can begin. The certification requirements are designed to ensure that personnel involved in the trial are committed to the study and proficient in study procedures, and that the center has satisfied regulatory requirements. Each center is required to obtain IRB approval for the study before they are certified to begin the trial.

### 8.2 Recruitment and Data Collection Period

Approximately 160,000 women deliver at MFMU Network centers annually. The APEX study database was queried to determine what proportion of all deliveries would be eligible for ARRIVE. A total of 17,960 pregnancies out of 115,502 or 15.5% satisfied the eligibility criteria. In addition, a pilot survey was conducted at four of the MFMU Network centers. A total of 204 women were queried to find out whether they would consent to this trial if it were presented to them. A total of 55% responded 'yes', 13% responded 'maybe' and 32% responded 'no'. Assuming only 20% percent of the 160,000 deliveries are available (due to, for example, certain sites or care providers not participating), 15.5% satisfying eligibility criteria and a 55% consent rate, this translates to 2700 patients per year. Assuming no limit on the ability to schedule inductions at 39 weeks, the study would easily be completed within 30 months.

Allowing an additional six months (i.e., 3 years in total), with only 30 of the 36 sites participating, translates to 67 patients per year per hospital (1.3 women per hospital per week) which should be feasible. Thus the overall recruitment goal is 167 women per month.

### **8.3 *Final Analysis***

After a two-month period for completion of data entry for the trial and close-out of the delivery and primary outcome, the data set will be locked and available for the primary and other main analyses.

## Appendix A Design Summary

### Induction in Nulliparous Women at 39 Weeks to Prevent Adverse Outcomes: A Randomized Controlled Trial

**OBJECTIVE:** To determine whether elective induction of labor in nulliparous women at 39 weeks improves adverse perinatal/neonatal outcome compared with expectant management.

<b>ORGANIZATION</b>		<b>SCHEDULED EVALUATIONS / DATA COLLECTION</b>	
Clinical Centers:	UAB, Ohio State, UTSW, Utah, Brown, Columbia, Case Western, UT-Houston, UNC, Northwestern, UTMB-Galveston, Colorado, Duke, Stanford, Magee, U Penn	Randomization:	<ul style="list-style-type: none"> <li>❖ Gestational age estimation</li> <li>❖ Digital cervical exam; Bishop score</li> <li>❖ Pregnancy, exposure and medical history</li> </ul>
Subcommittee:	William Grobman, MD (Chair)	Post-randomization:	<ul style="list-style-type: none"> <li>❖ Weekly visit with provider (expectant management group)</li> </ul>
<b>DESIGN</b>		Delivery:	<ul style="list-style-type: none"> <li>❖ Patient-centered outcomes questionnaire</li> <li>❖ Delivery and neonatal data</li> <li>❖ Central chart review for primary outcome</li> </ul>
Major Eligibility Criteria:	<ul style="list-style-type: none"> <li>❖ Singleton gestation</li> <li>❖ Gestational age 38<sup>0</sup> to 38<sup>6</sup> wks</li> <li>❖ Nulliparous</li> </ul>	Postpartum:	<ul style="list-style-type: none"> <li>❖ Patient-centered outcomes questionnaire</li> </ul>
Groups:	<ul style="list-style-type: none"> <li>❖ Induction of labor at 39 weeks</li> <li>❖ Expectant management with induction by 42 weeks, if undelivered</li> </ul>	<b>MANAGEMENT PROTOCOL</b>	
Random Allocation:	Standard urn design; 1:1 allocation	Induction Group	<ul style="list-style-type: none"> <li>❖ Induction via oxytocin at 39<sup>0</sup>-39<sup>4</sup> wks.</li> <li>❖ If unfavorable cervix (modified Bishop score &lt; 5) start with cervical ripening</li> </ul>
Level of Masking:	Unmasked	Expectant Mgmt Group	<ul style="list-style-type: none"> <li>❖ Continue pregnancy until at least 40<sup>5</sup> wks (unless indication for delivery)</li> <li>❖ Start antepartum fetal testing no later than 41<sup>6</sup></li> <li>❖ All patients induced by 42<sup>2</sup> wks</li> </ul>
Stratification:	<ul style="list-style-type: none"> <li>❖ Clinical site</li> </ul>	<b>OUTCOME MEASURES</b>	
Sample Size:	<ul style="list-style-type: none"> <li>❖ 6000</li> </ul>	Primary:	<ul style="list-style-type: none"> <li>❖ Neonatal adverse outcome/fetal death</li> </ul>
Assumptions:	<ul style="list-style-type: none"> <li>❖ Outcome event=perinatal death /neonatal adverse outcome</li> <li>❖ Expectant management event rate = 3.5%</li> <li>❖ Induction of labor group event rate = 2.28% (38% reduction)</li> <li>❖ Type 1 error = 5% two sided</li> <li>❖ Power =85%</li> </ul>	Major Secondary:	<ul style="list-style-type: none"> <li>❖ Cesarean delivery</li> <li>❖ Maternal adverse outcomes</li> <li>❖ Gestational age at delivery</li> <li>❖ Utilization of medical resources</li> </ul>
Interim Analysis:	<ul style="list-style-type: none"> <li>❖ Lan-DeMets group sequential method</li> </ul>	TIMETABLE (as originally planned)	
		Enrollment	<ul style="list-style-type: none"> <li>❖ Oct 2013 to Sep 2016</li> </ul>
		Data Collection	<ul style="list-style-type: none"> <li>❖ Oct 2013 to Nov 2016</li> </ul>
		Closeout	<ul style="list-style-type: none"> <li>❖ Dec 2016 to Mar 2017</li> </ul>
		TIMETABLE (revised)	
			<ul style="list-style-type: none"> <li>❖ Oct 2013 to Oct 2017</li> <li>❖ Oct 2013 to Dec 2017</li> <li>❖ Jan 2018 to Apr 2018</li> </ul>

## **Appendix B    Sample Informed Consent Form**

**Research Study Title:** A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

**Sponsor:** Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)

**Principal Investigator:** \_\_\_\_\_ **Phone** (\_\_\_\_) \_\_\_\_ - \_\_\_\_

### **Introduction**

You are invited to take part in a research study. This consent form provides the information about the risks and benefits of the study. A member of the research team is available to answer your questions and to provide further explanations. You are free to choose whether or not you will take part in the study. If you agree to take part in the research, you will be asked to sign this consent form. This process is known as informed consent.

### **Research Purpose**

You are being invited to participate because you are pregnant, having your first baby, and are planning to labor. The goal of the study is to determine whether coming to the hospital and having your labor started with medicine (i.e., labor induction) at 39 weeks of pregnancy can improve the baby's health at birth when compared with waiting for labor to start on its own.

Many doctors wait until 41 weeks for labor to start on its own. However, some studies, but not all, have shown that being induced at 39 weeks of pregnancy may improve the baby's outcome. Some older studies have suggested a higher risk of cesarean, but other recent studies have not shown this increased risk. No studies like this one have been done before in the United States. This study is planning to enroll 6,000 women across the country. Half of the women will be induced at about 39 weeks of gestation and half will have the existing prenatal care (that is, waiting for start of labor).

### **Procedures**

If you consent to the study, when you are within one to two weeks of your due date, you will be randomized (like flipping a coin) to one of two groups. In one group (the "induction of labor" group), you will have your labor started through the use of medicine within a few days of reaching 39 weeks of pregnancy. Depending upon how open your cervix is (the cervix is the opening to your uterus or birth canal), your doctor will decide the best way to start your labor. In the other group (the "expectant management group") you will continue with your pregnancy until either you begin labor or your care provider determines that you need to be delivered or you reach 41-42 weeks of gestation (1-2 weeks after your due date).

Regardless of which group you are in, your care provider will check your cervix (the opening of your uterus or birth canal) during a pelvic examination. This may have already been done as a part of regular care within three days of your being randomized in which case it would not have to be repeated. If you receive medication to help open your cervix or start your labor, your baby's heart rate will be monitored all the time you are receiving the medication and when you are in labor. Once you receive medication to help open your cervix or start your labor you should expect to stay in the hospital until delivery. All other care during your pregnancy and during labor will be at the discretion of your care provider.

After delivery, research staff will review your medical chart for clinical and outcome information such as any treatments or medicines given during labor and whether you had a vaginal delivery or cesarean section. They will also review the medical chart of your newborn. The research team will collect information regarding your hospital course and that of your newborn until hospital discharge.

You will be asked two questions about the pain you experienced during childbirth and asked to fill out one questionnaire soon after your baby is born. The questionnaire will be about how you felt about the process of labor and giving birth. Six weeks after your baby is born, research staff will contact you to find out about any unplanned hospital or clinic visits for you or your baby and you will be asked to fill out the same questionnaire about the process of labor again.

### **Possible Risks**

During labor induction, the same types of complications that can occur during any labor can occur. At present, it is not known whether labor induction at 39 weeks is associated with a greater chance of cesarean delivery. Some older studies have suggested a higher risk of cesarean, but other recent studies have not shown this increased risk.

### **Benefits**

If you decide to take part in this research study, you and your baby may not directly benefit. Your participation may help doctors determine the best time to plan for delivery in the future.

### **Alternative Procedures**

The alternative to this study is not to participate. Women who do not take part in this study will continue with their pregnancies until either they begin labor or their care provider determines there is a reason that they need to be delivered before labor begins (i.e., the standard care during pregnancy).

### **Costs**

There will be no cost to you to take part in the research study. The costs of your labor, delivery and care after delivery will be billed to you or your insurance company in the usual manner.

### **Compensation**

(THIS SECTION WILL BE CENTER SPECIFIC.) You will be paid \$XX to compensate you for the time and travel associated with the research study.

### **Payment for Injury or Harm**

(THIS SECTION WILL BE CENTER SPECIFIC.) This hospital is not able to offer financial compensation or absorb the costs of medical treatment in the event of injury resulting from the research. In the event of such injury, treatment will be provided but it is not provided free of charge. Since this is a research study, payment for any injury resulting from your participation in this research study may not be covered by some health insurance plans.

### **Right to Withdraw From the Research Study**

This study is voluntary and it is up to you to decide whether or not you want to participate. You are free to withdraw your consent and stop taking part in this research study at any time without giving a reason. Refusal to take part or the decision to withdraw from the study will involve no penalty or loss of benefits to which you are otherwise entitled. Your refusal will not affect your legal rights or quality of health care that you will receive at this hospital. Any significant new information which becomes available during your participation in this research, and which may affect your health, safety, or willingness to continue in this research study, will be given to you.

### **Right of the Investigator to Withdraw**

The researchers of this institution or the National Institutes of Health can withdraw you from this study without your approval. A possible reason for withdrawal could be the early termination of the study by the National Institutes of Health.

### **Confidentiality**

You have the right to privacy. All information obtained from this research that can be identified with you will remain confidential within the limits of the law.

The medical information collected on you for this research study will come from your medical record and from information you give the nurse, such as your previous pregnancies, height, weight, and whether you drink or smoke. Other information collected about you includes whether you are married, whether you have a job, and type of medical insurance. If we lose track of you, study staff may collect information from the internet including social network sites in order to find your contact information.

The information collected for this research study will be held at the data coordinating center (George Washington University Biostatistics Center in Rockville, Maryland) in a database consisting of information from all of the participants in this study. Your information in the database will **only** be used for statistical analysis and may appear in scientific publications but will not identify you. The information at the data coordinating center does **not** include your name, address, social security number, hospital number, date of birth or any other personal identifiers. Instead the data center will use a unique code for each person consisting of a number and the first letter of your first name. The key to the code linking the data to you will be kept here in a locked file. Only the research study staff employed for this study at this hospital will have access to the key to the code.

The following individuals and/or agencies will be able to look at and copy your research records:

- The investigator, study staff and other medical professionals who may be evaluating the study.
- Authorities from this institution, including the Institutional Review Board (IRB) which is a group of people who are responsible for making sure the rights of participants in research are respected. Members or staff of the IRB at this medical center may also contact you about your experience with this research. You do not have to answer any questions asked by the representative of the board.
- The Office for Human Research Protections (OHRP)
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) which sponsors this study, including persons or organizations working with the sponsors, such as the data coordinating center, the George Washington University Biostatistics Center in Rockville, Maryland.

A copy of your or your baby's medical chart may also be sent to research investigators at one of the other enrolling centers or the data coordinating center for review. If your chart is sent, identifying information, such as name, address, social security number, or hospital number will be removed.

The results of this research study will be provided to the sponsor, NICHD, (and/or its representatives). In addition, data from this study will be put in a public data set that will be available to other research investigators. This public data set will not contain any identifying patient data.

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

This permission does not end unless you cancel it, even if you leave the study. You can cancel this permission any time except where a healthcare provider has already used or released your health information, or relied on your permission to do something. Even if you cancel this authorization, the researchers may still use and disclose protected health information (PHI) they already have obtained about you as necessary to maintain the integrity or reliability of the research. However, no new PHI will be collected from you after you revoke your authorization.

To cancel your authorization, you will need to send a letter to Dr. \_\_\_\_\_ of the \_\_\_\_\_ stating that you are canceling your authorization. This letter must be signed and dated and sent to this

address: \_\_\_\_\_. If you are unable to write a letter ask one of the research staff to provide you with a letter that must be signed, dated, and sent to the above address. A copy of this revocation will be provided to the Study Doctor and his or her research team. Not signing this form or later canceling your permission will not affect your health care treatment outside the study, payment for health care from a health plan, or ability to get health plan benefits.

Your protected health information will be treated confidentially to the extent permitted by applicable laws and regulations. Federal law may allow someone who gets your health information from this study to use or release it in some way not discussed in this section and no longer be protected by the HIPAA Privacy Rule.

By signing this form you authorize the Study Doctor and members of the research team to use and share with others (disclose) your PHI for the purpose of this study. If you do not wish to authorize the use or disclosure of your PHI, you cannot participate in this study because your PHI is necessary to conduct this study.

### **Questions**

The researchers are available to answer your questions about this research. A representative of the Institutional Review Board is also available to answer questions about your rights as a participant in research or to answer your questions about an injury or other complication resulting from your participation in this research study.

If you have questions or are hurt while taking part in this research study, you should contact \_\_\_\_\_ at (\_\_\_\_) \_\_\_\_-\_\_\_\_.

If you have any questions about the informed consent process or any other rights as a research subject, please contact \_\_\_\_\_, at (\_\_\_\_) \_\_\_\_-\_\_\_\_. \_\_\_\_\_.

### **Signatures**

By signing below, you indicate that you have read this consent form, the study has been explained to you, your questions have been answered, and you agree to take part in this study. You do not give up any of your legal rights by signing this form. A copy of this consent form will be given to you.

The investigator or study team may wish to contact you in the future to request permission for additional research. Please initial the appropriate statement to indicate whether or not you give permission for future contact.

YES \_\_\_\_\_ I give permission to be contacted in the future for research purposes.

NO \_\_\_\_\_ I do not give permission to be contacted in the future for research purposes.

\_\_\_\_\_  
Participant  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Person Obtaining Consent  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date



**ASSENT FOR FEMALES UNDER 18 YEARS of AGE (if required by Center IRB):**

I agree \_\_\_\_\_ I do not agree \_\_\_\_\_ to participate in this study.

This has been explained to me by \_\_\_\_\_.

\_\_\_\_\_  
Signature of Minor

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name of Subject

\_\_\_\_\_  
Age

Please provide either one or both parental signatures as instructed by your IRB.

\_\_\_\_\_  
Signature of Mother/Guardian

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Father/Guardian

\_\_\_\_\_  
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' Name  
(Print Name)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

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## ARRIVE Trial Protocol Changes

There were 3 modifications to the protocol:

1. December 23, 2014
2. April 27, 2017
3. July 20, 2017

### ARRIVE Protocol Changes – December 23, 2014

1. Section 3.4.2 Gestational Age Determination - the dating criteria were updated for a sure last menstrual period (LMP) to use criteria proposed by the American Congress of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine and the Society for Maternal-Fetal Medicine (Committee opinion no 611: method for estimating due date. Obstet Gynecol 2014;124:863-6). The changes compare the gestational age by LMP and by the earliest dating ultrasound:

<b>Gestational age at first ultrasound by LMP</b>	<b>Ultrasound method of measurement</b>	<b>Ultrasound agreement with LMP</b>
Up to 8 weeks 6 days	CRL	± 5 days
9 weeks 0 days to 13 weeks 6 days	CRL	± 7 days
14 weeks 0 days to 15 weeks 6 days	Per institution	± 7 days
16 weeks 0 days to 20 weeks 6 days	Per institution	± 10 days

2. Section 3.4.3 Exclusion Criteria: Added breech presentation as an exclusion criterion.

### ARRIVE Protocol Changes – April 27, 2017

1. The following research questions and secondary outcomes were deleted from the protocol to keep the primary manuscript more focused and allow secondary papers to focus on these outcomes.
  - a. Section 3.2 Secondary Research Questions – deleted:
    - i. Does elective induction of labor in nulliparous women at 39 weeks modify the patient-centered outcomes listed in section 4.7.2?
  - b. Section 4.7.2 Maternal Secondary Outcomes (and Appendix A Design Summary) – deleted:
    - i. Patient-reported outcomes including feelings of control during childbirth, as measured by the Labour Agency Scale,<sup>50</sup> and two questions regarding pain experienced during childbirth using a visual analog scale<sup>51</sup>
  - c. Section 4.7.3 Fetal and Neonatal Secondary Outcomes – deleted:
    - i. Macrosomia > 4500 g, large for gestational age (LGA) defined as > 90<sup>th</sup> percentile weight for gestational age, assessed specifically by sex and race of the infant based on United States birth certificate data<sup>52</sup>
    - ii. Small for gestational age defined as < 5<sup>th</sup> and < 10<sup>th</sup> percentile weight for gestational age, assessed specifically by sex and race of the infant based on United States birth certificate data<sup>52</sup>

- d. Section 4.7.4 Utilization of Medical Resources – deleted:
  - i. Number of clinic visits post randomization to admission for delivery
  - ii. ER/urgent care/triage visits post randomization to delivery
  - iii. Non-stress tests, biophysical profiles (BPPs), modified BPPs, ultrasounds done other than BPP, Doppler, contraction stress tests
  - iv. Epidural use
  - v. Intrauterine pressure catheter (IUPC) or fetal scalp electrode placement
  - vi. Use of induction and ripening agents, maximum dose of oxytocin
  - vii. Antepartum hospital admission
  - viii. Length of neonatal intensive care unit or intermediate care stay
  - ix. Post discharge resource utilization including inpatient and outpatient visits for mother or baby
2. Section 3.2 Secondary Research Questions – clarification regarding when subgroup analyses would be performed, to be consistent with the analysis plan:
  - a. Added: ‘If the two groups show a difference in the incidence of the primary outcome or cesarean’ before ‘Does the proposed effect of elective induction of labor in nulliparous women at 39 weeks vary according to any of the subgroups listed in section 5.5?’
3. Section 4.7.1 Primary Outcome – clarification of the definition of the primary component intracranial hemorrhage to include:
  - a. Intraventricular hemorrhage grades III and IV, subgaleal hemorrhage, subdural hematoma, or subarachnoid hematoma
4. Section 5.5 Analysis Plan:
  - a. Added ‘or cesarean’ to the following sentences:
    - i. If the two groups show a difference in the incidence of the primary outcome **or cesarean**, interactions will be evaluated and subgroup analyses conducted to determine whether the effect prevails throughout particular subgroups of patients.
    - ii. Assuming for this trial that the composition is 25% African-American and 30% Hispanic, similar to the ongoing STAN trial, there is limited power (40-50%) to detect a 50% reduction in the primary outcome **or cesarean** in the separate subgroups.
  - b. Added the following subgroups:
    - i. Maternal age (< 35 and ≥ 35 years)
    - ii. Admitting provider specialty
  - c. Added the following paragraph regarding admitting provider specialty subgroup analysis:
    - i. Although admitting provider specialty is not a baseline variable, this variable will be evaluated for subgroup analysis if the two groups show a difference in the incidence of the primary outcome or cesarean, and if the test for interaction is significant. Elective induction of labor may be perceived as an intervention more likely utilized by obstetricians than by midwives, therefore it is important to demonstrate whether a treatment effect is present among patients treated by obstetricians and among patients treated by midwives.

5. Appendix A Design Summary:
  - a. Added two clinical centers: Magee and U Penn
  - b. Enrollment period extended to October 2017
6. Throughout – changed ‘Program Scientist’ to ‘Project Scientist’

#### ARRIVE Protocol Changes – July 20, 2017

1. Section 4.7.1 Primary Outcome - wording of a few components of the primary outcome was changed to be consistent with the data forms:
  - a. ‘cardiorespiratory support’ was changed to ‘cardiopulmonary resuscitation’
  - b. ‘facial nerve injury’ was changed to ‘facial nerve palsy’
  - c. ‘subgaleal hemorrhage’ was changed to ‘subgaleal hematoma’
2. Section 4.7.2 Maternal Secondary Outcomes - typographical errors corrected:
  - a. Removed an ‘and’ and added an ‘or’ to the following sentence: ‘Other surgical interventions such as uterine compression sutures, uterine artery ligation, embolization, ~~and~~ hypogastric ligation, **or** balloon tamponade’
3. Section 4.7.3 Fetal and Neonatal Secondary Outcomes - definition of a secondary outcome was changed to be consistent with the manual, and a typographical error was corrected:
  - a. ‘Hypoglycemia (glucose < 40 mg/%) requiring IV therapy’ was changed to ‘Hypoglycemia (glucose < 35 mg/dl) requiring IV therapy’