

October 4, 2019

Study Title: Cervical Pessary to Prevent Preterm Birth in Singleton Pregnancies With a Sonographically Measured Short Cervix

FDA IDE G140219  
NCT02357394

This study was an open label, randomized controlled trial which was designed to determine if the use of the Arabin cervical pessary would reduce the incidence of preterm birth. At the time of conception, our study differed from other studies regarding the Arabin cervical pessary in that we allowed the use of vaginal progesterone and/or cervical cerclage in the control group. In essence, our study compared the community care standard of practice in our area with the use of the Arabin cervical pessary for an ultrasound diagnosed short cervix.

Our study required an FDA IDE application, assigned number G140219, and registration on clinicaltrials.gov as NCT02357394. Our first patient was enrolled 7/1/2015. Our last patient was enrolled 7/4/2016. Our last data entry occurred in November 2016. We subsequently were unable to enroll any further patients due to low interest. We decided to close the study formally 4/4/2019.

Results were entered to clinicaltrials.gov on 10/4/2019. Due to low number of enrolled subjects (n=7), only raw data is reported. No statistical tests were run.

Signed,

Gene Lee MD  
Assistant Professor  
MFM/OBGYN  
The University of Kansas Health System

**Sponsor: GENE T. LEE, MD**

**Clinical Research Protocol**

**Cervical pessary to prevent preterm birth in singleton pregnancies  
with a sonographically measured short cervix: an open-label  
randomized controlled trial**

Protocol Number:	Cerclage Pessary
Version Date:	4/24/2015
Investigational Device:	Arabin Pessary
IDE Number:	G140219
Study Phase:	II
Sponsor-Investigator:	Gene T. Lee, MD Assistant Professor Department of Obstetrics and Gynecology University of Kansas Medical Center
Funding Organization:	Unfunded
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**LIST OF ABBREVIATIONS**

<b>AE</b>	adverse event
<b>CFR</b>	Code of Federal Regulations
<b>CRF</b>	case report form
<b>DMC</b>	Data Monitoring Committee
<b>DSMB</b>	Data Safety Monitoring Board
<b>FDA</b>	Food and Drug Administration
<b>GCP</b>	Good Clinical Practice
<b>HIPAA</b>	Health Insurance Portability and Accountability Act of 1996
<b>HSC</b>	Human Subjects Committee, KUMC Local IRB
<b>ICF</b>	informed consent form
<b>ICH</b>	International Conference on Harmonisation
<b>IEC</b>	Independent Ethics Committee
<b>IRB</b>	Institutional Review Board
<b>QC</b>	Quality Control
<b>PI</b>	Principal Investigator
<b>UADE</b>	unanticipated adverse device effect

**PROTOCOL SYNOPSIS**

<b>TITLE</b>	Cervical pessary to prevent preterm birth in singleton pregnancies with a sonographically measured short cervix: an open-label randomized controlled trial
<b>SPONSOR</b>	Gene T. Lee, MD
<b>FUNDING ORGANIZATION</b>	Unfunded
<b>NUMBER OF SITES</b>	1; University of Kansas Medical Center 2. Medical University of South Carolina
<b>RATIONALE</b>	The Arabin cervical pessary has emerged as a promising treatment for cervical insufficiency. A recent Spanish RCT demonstrated reduced preterm births with the use of the Arabin pessary. The results of this study pessary should also be confirmed here in the USA.
<b>STUDY DESIGN</b>	Open-label, randomized, controlled trial
<b>PRIMARY OBJECTIVE</b>	To determine if the Arabin pessary can reduce preterm birth before 37 weeks in patients with a short cervix
<b>SECONDARY OBJECTIVES</b>	To determine if the Arabin pessary can reduce maternal and neonatal morbidity
<b>NUMBER OF SUBJECTS</b>	256
<b>SUBJECT SELECTION CRITERIA</b>	<p><u>Inclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>• singleton pregnancy</li> <li>• age 18 – 45y</li> <li>• cervical length &lt; 25 mm measured by transvaginal ultrasound prior to 23 weeks 0 days</li> <li>• Agrees to refrain from sexual intercourse</li> </ul> <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>• major fetal anomalies</li> <li>• painful regular uterine contractions</li> <li>• active vaginal bleeding</li> <li>• ruptured membranes</li> <li>• evidence of chorioamnionitis or other maternal/fetal infectious morbidity</li> <li>• placenta previa</li> <li>• current progesterone therapy</li> <li>• cervical cerclage in situ</li> <li>• visual cervical dilation of 2 cm or greater with visible amnion/chorion</li> <li>• significant maternal-fetal complications (insulin dependent diabetes mellitus, systemic lupus erythematosus with nephritis, chronic hypertension, red cell alloimmunization, drug abuse)</li> </ul>
<b>INVESTIGATIONAL DEVICE / INTENDED USE</b>	Device: Arabin pessary The intended use is to treat women with cervical insufficiency characterized by a cervix that is too short for gestation as objectively measured on transvaginal ultrasound.

<b>CONTROL GROUP OR OTHER STUDY ARMS (if applicable)</b>	Device: None Patients randomized to the control group will receive standard of care for their condition.
<b>Duration of Subject Participation and Estimated Total Length of Study</b>	Subjects' participation in the study will last about 7 months.  Based on the number of patients KUMC and MUSC examine in a year for cervical length screening in the 2 <sup>nd</sup> trimester, the study will take 4 years to complete with 80% accrual. We expect a loss to follow up rate of 5%.
<b>PRIMARY ENDPOINT</b>	<ul style="list-style-type: none"> <li>• Preterm birth less than 37 weeks 0 days gestation</li> </ul>
<b>SECONDARY ENDPOINTS</b>	<ul style="list-style-type: none"> <li>• Neonatal composite morbidity – fetal or neonatal death, respiratory distress syndrome (RDS), chronic lung disease, periventricular lucency, periventricular leukomalacia, intraventricular hemorrhage grade 3 or 4, necrotizing enterocolitis, early-onset-culture-proven sepsis</li> <li>• Neonatal length of stay</li> <li>• Neonatal NICU admission</li> <li>• Total NICU days</li> <li>• Duration of ventilator support</li> <li>• retinopathy of prematurity (ROP) requiring treatment</li> <li>• birthweight &lt; 1500g and &lt; 2500g</li> <li>• preterm birth &lt; 34 weeks</li> <li>• gestational age at delivery</li> <li>• use of tocolysis</li> <li>• use of antenatal steroids</li> <li>• chorioamnionitis</li> <li>• vaginal bleeding</li> <li>• preterm premature rupture of membranes</li> <li>• cesarean delivery</li> </ul>
<b>OTHER EVALUATIONS</b>	Maternal age, body mass index, obstetric history, smoking history, gestational age at randomization, cervical length at randomization, sludge at randomization
<b>SAFETY EVALUATIONS</b>	Patients randomized to the pessary group will be examined for vaginal and cervical infections. Any found infections are treated, and pessary insertion is delayed a week. After insertion, patients are examined for urinary retention. If found, a smaller pessary is inserted. Patients are seen in clinic every 2 weeks, vaginal swabs are examined if symptoms of infection are present, and a questionnaire about symptoms is completed. Pessaries are removed if there is active vaginal bleeding, risk of preterm labor with persistent contractions, or severe patient discomfort.
<b>PLANNED INTERIM ANALYSES</b>	The data will be reviewed every 6 months by the designated medical monitor for the study, Vishal Pandey MD (neonatologist). The medical monitor is specifically chosen outside of the department of OBGYN to allow for objectivity. Adverse events which would requires immediate suspension of study for review would include an excess of 1 maternal death, 1 maternal ICU admission for sepsis, or 2 perinatal deaths in the <b>pessary</b> group. Unanticipated adverse events will be reported immediately to the Human Subjects Committee (HSC) and the FDA, and its recommendations for temporary cessation or continuation of the study will be followed. If an excess of 4 perinatal deaths occur in the <b>pessary</b> group, the study should be concluded.

<b>STATISTICS</b> <b>Primary Analysis Plan</b>	<p>The Research hypothesis is that proportion of preterm deliveries before 37 weeks 0 days gestation is reduced in the pessary group as compared to the control group. The primary endpoint and the categorical outcomes that are part of the secondary endpoints will be reported using frequency counts and proportions. For the secondary endpoints that are continuous variables, summary statistics such as mean and standard deviation, or median and inter-quartile range will be reported based on whether the assumption of normality is justified. A chi-square test (or a Fisher's exact test) will be used to perform statistical comparison of proportions across the two groups. Likewise, comparisons for continuous outcomes will be done using a two-sample t-test (or Wilcoxon Rank Sum test) as will be deemed necessary. For gestational age, we will also compare the Kaplan Meier survival curves of the two groups (control and pessary) using the logrank test. Level of significance for all statistical tests will be set at 0.05.</p>
<b>Rationale for Number of Subjects</b>	<p>Based on KUMC and MUSC hospital data, the proportion of preterm births before 37 weeks 0 days gestation in patients with short cervixes is 30%. In order to detect a reduction in half to 15%, a sample size of 242 will be required to have power of 80% using a two-sided z-test assuming pooled variances. Level of significance is set at 0.05. We anticipate a loss to follow up rate of 5%. We expect to enroll 256 subjects.</p>



## 1.0 PURPOSE OF THE INVESTIGATION

### 1.1 Name of investigational device

Device Name: Arabin pessary

Company/Manufacturer: Dr. Arabin GmbH & Co. KG

Address: Alfred-Herrhausen-Str. 44 – 58455 Witten

### 1.2 Intended use of the investigational device

The intended use is to treat women with cervical insufficiency characterized by a cervix that is too short for gestation as objectively measured on transvaginal ultrasound.

### 1.3 Report of Prior Investigations

#### 1.3.1 General

*The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.*

The Arabin pessary was first described clinically for the treatment of cervical insufficiency in a 1990 article published in German (6). Although good outcomes were obtained, it would be 13 more years before another study reintroduced the Arabin pessary for the treatment of cervical insufficiency (2). This 2003 pilot project consisting of 46 at risk patients again demonstrated improved outcomes characterized by a 32 day prolongation of gestation in singletons and an 18 day prolongation of gestation in twins compared to patients without pessary. The authors acknowledged a larger RCT needed to be done. In 2012, a large RCT including 385 singleton pregnancies was concluded demonstrating the Arabin pessary prolonged pregnancy and reduced the rate of preterm birth in women with a singleton and a sonographically short cervix (2). For patients with a cervical length < 25 mm at 20-23 weeks gestation, the pessary reduced the prevalence of preterm birth < 34 weeks from 27% to 6%. Three other cohort studies, 2 retrospective and 1 prospective, provide supportive evidence of prolongation of pregnancy when the pessary is used (1,3,4). One study investigated a particularly high-risk population consisting of twin pregnancies complicated by twin-to-twin transfusion syndrome and a sonographically short cervix. In 2013, a large RCT of 808 multiples (ProTWIN) did not find evidence of benefit in the pessary group. This trial did not require an inclusion criteria of a short cervix, and a significant number of patients in the pessary group either did not receive the pessary (6%) or had the pessary removed prior to 28 weeks (57 patients, 14%). Some of the reasons for removal suggest poor insertion or provider anxiety (lost pessary 7, contractions 5, pain 17). A subgroup analysis suggested that there was benefit for multiple gestations where the cervical length was at the 25<sup>th</sup> percentile (38mm).

#### 1.3.2 Specific Content

- a) *A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.*

1: Carreras E, Arevalo S, Bello-Munoz JC, Goya M, Rodo C, Sanchez-Duran MA, Peiro JL, Cabero L. Arabin cervical pessary to prevent preterm birth in severe twin-to-twin transfusion syndrome treated by laser surgery. *Prenat Diagn*. 2012 Dec;32(12):1181-5. doi: 10.1002/pd.3982. Epub 2012 Oct 11. PubMed PMID: 23055333.

2: Goya M, Pratcorona L, Merced C, Rodo C, Valle L, Romero A, Juan M, Rodriguez A, Munoz B, Santacruz B, Bello-Munoz JC, Llurba E, Higuera T, Cabero L, Carreras E; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet*. 2012 May 12;379(9828):1800-6. Epub 2012 Apr 3. Erratum in: *Lancet*. 2012 May 12;379(9828):1790. PubMed PMID: 22475493.

3: Ting YH, Lao TT, Law LW, Hui SY, Chor CM, Lau TK, Leung TY. Arabin cerclage pessary in the management of cervical insufficiency. *J Matern Fetal Neonatal Med*. 2012 Aug 22. [Epub ahead of print] PubMed PMID: 22871155.

4: Sieroszewski P, Jasinski A, Perenc M, Banach R, Oszukowski P. The Arabin pessary for the treatment of threatened mid-trimester miscarriage or premature labour and miscarriage: a case series. *J Matern Fetal Neonatal Med*. 2009 Jun;22(6):469-72. PubMed PMID: 19530009.

5: Arabin B, Halbesma JR, Vork F, Hubener M, van Eyck J. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? *J Perinat Med*. 2003;31(2):122-33. PubMed PMID: 12747228.

6: Quaas L, Hillemanns HG, du Bois A, Schillinger H. [The Arabin cerclage pessary--an alternative to surgical cerclage]. *Geburtshilfe Frauenheilkd*. 1990 Jun;50(6):429-33. German. PubMed PMID: 2198191.

7. Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, Brons J, Duvekot H, Bijvank BN, Franssen M, Gaugler I, de Graaf I, Oudijk M, Papatsonis D, Pernet P, Porath M, Scheepers L, Sikkema M, Sporken J, Visser H, van Wijngaarden W, Woiski M, van Pampus M, Mol BW, Bekedam D. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet*. 2013 Oct 19;382(9901):1341-9. doi: 10.1016/S0140-6736(13)61408-7. Epub 2013 Aug 5. PubMed PMID: 23924878.

8. Liem SM, van Baaren GJ, Delemarre FM, Evers IM, Kleiverda G, van Loon AJ, Langenveld J, Schuitemaker N, Sikkema JM, Opmeer BC, van Pampus MG, Mol BW, Bekedam DJ. Economic analysis of use of pessary to prevent preterm birth in women with multiple pregnancy (ProTWIN trial). *Ultrasound Obstet Gynecol*. 2014 Sep;44(3):338-45. doi: 10.1002/uog.13432. Epub 2014 Aug 7. PubMed PMID: 24898103.

## 1.4 Objectives of the clinical investigation

### 1.4.1 Primary objective

- Frequency of preterm deliveries < 37 weeks 0 days gestation

#### 1.4.2 Secondary Objectives

- Neonatal composite morbidity – fetal or neonatal death, respiratory distress syndrome (RDS), chronic lung disease, periventricular lucency, periventricular leukomalacia, intraventricular hemorrhage grade 3 or 4, necrotizing enterocolitis, early-onset-culture-proven sepsis
- Neonatal length of stay
- Neonatal NICU admission
- Total NICU days
- Duration of ventilator support
- retinopathy of prematurity (ROP) requiring treatment
- birthweight < 1500g and < 2500g
- preterm birth < 34 weeks
- gestational age at delivery
- use of tocolysis
- use of antenatal steroids
- chorioamnionitis
- vaginal bleeding
- preterm premature rupture of membranes
- cesarean delivery

#### 1.5 Anticipated duration of the clinical investigation

KUMC examines approximately 1900 patients in a year for cervical length screening in the 2<sup>nd</sup> trimester (our standard of care for more than 6 years). Approximately 45 patients a year have cervical lengths < 25 mm.

MUSC examines approximately 2-3 thousand patients per year with cervical length screening. Approximately 60 patients a year have cervical lengths <25 mm.

We expect 80% accrual rate into the study. The expected duration of the study is ~ 4 years.

## 2.0 CLINICAL PROTOCOL

### 2.1 Protocol number

KUOBGYN001: Can the Arabin pessary prevent preterm birth in singleton pregnancies that have a short cervix?

### 2.2 Protocol version number and date

April 24, 2015

## **2.3 Study design**

### **2.3.1 General study design**

This study is a randomized controlled trial. It is not blinded to either investigator or patient.

## **2.4 Subject selection**

### **2.4.1 General characteristics of the proposed subject population(s)**

The patients enrolled into this study are < 23 weeks 0 days pregnant and will have a cervical length < 25 mm detected by transvaginal ultrasound performed during universal screening at each institution participating in this trial. These patients are seeking care at a tertiary care center, and in general have a higher risk profile compared to the community due to presence of maternal disease such as diabetes or hypertension or obstetric history such as prior preterm birth.

The Arabin pessary is designed to reduce preterm birth in pregnant patients with a short cervix. The suggested patients for this clinical trial exactly match the type of patients treated by the Arabin pessary.

### **2.4.2 Anticipated number of research subjects**

We plan to enroll 256 subjects in this study on a 1:1 basis. Our research hypothesis is the proportion of preterm deliveries before 37 weeks 0 days gestation is reduced in the pessary group as compared to the control group. Based on records of patients currently treated for short cervixes here at KUMC and MUSC over the past year, the number of preterm birth before 37 weeks gestation is 30%. In order to detect a reduction in half to 15%, we require a sample size of 242 subjects for analysis. We experience about a 5% loss to follow up rate. We will use an intent-to-treat principle for analyzing the outcomes of the trial. All enrolled patients will provide informed consent for study participation.

### **2.4.3 Inclusion criteria**

- Singleton pregnancy
- Age 18 – 45y
- Cervical length < 25 mm measured by transvaginal ultrasound prior to 23 weeks 0 days
- Agrees to refrain from sexual intercourse

### **2.4.4 Exclusion criteria**

- 
- Major fetal anomalies
- Painful regular uterine contractions
- Active vaginal bleeding
- Ruptured membranes

- Evidence of chorioamnionitis or other serious maternal/fetal infectious morbidity
- Placenta previa
- Current progesterone therapy
- Cervical cerclage in situ
- Visual cervical dilation of 2 cm or greater with visible amnion/chorion
- Significant maternal-fetal complications (insulin dependent diabetes mellitus, systemic lupus erythematosus patients with nephritis, chronic hypertension, red cell alloimmunization, drug abuse)

The PECEP trial (Goya et al 2012) excluded patients with a history of prior cone biopsy. We feel that a history of prior cone biopsy is exactly the type of patient the pessary was designed to treat, a pregnancy at increased risk of preterm delivery due to a shortened cervix. Anatomically, prior cone surgery can lead to a shortened cervix anatomically, which would preclude successful placement of the pessary. Clearly, if a pessary cannot be placed, it will have no effect on outcomes. On the other hand, if the cone surgery has not precluded the placement of the pessary due to anatomy, then we feel that these patients should be included in the study.

Significant maternal-fetal complications are listed as an exclusion since they have increased risk of iatrogenic preterm delivery for reasons that have no relationship with the presence or absence of the pessary. Insulin dependent diabetes with significant proteinuria, lupus patients with nephritis, chronic hypertensives with proteinuria all have increased risks for preeclampsia, intrauterine growth restriction, placental abruption and stillbirth which would impact the outcomes recorded in this study.

## **2.5 Study procedures**

### **2.5.1 Screening procedures**

Patients are identified for the study by universal cervical length screening performed by ultrasound during the 2<sup>nd</sup> trimester. Once identified, patients are approached by study investigators who are authorized to obtain informed consent. The counseling will take place in the privacy of the ultrasound suite or a private clinic room. Both a medical history and physical exam are performed to verify if a patient meets criteria for enrollment in the study. The physical exam includes a sterile speculum exam which investigates for vaginal or cervical infections in symptomatic patients.

### **2.5.2 Study treatment or diagnostic product procedures**

The treatment proposed in this study is the placement of the Arabin pessary around the cervix. This device currently does not have FDA approval. The company which manufactures the device in Europe has applied for FDA license. A consultant report by NAMSA which describes the device, classification, safety, toxicity, and testing is included in this application.

Patients in the experimental arm will have the Arabin pessary placed at time of enrollment. First, they are assessed for uterine contractions by tocodynamometer. To repeat, if symptoms of genital infection are present, the investigator will perform a sterile speculum exam and a wet mount and cervical cultures for gonorrhea/chlamydia will be obtained. Any symptomatic infections are treated, and the pessary insertion is delayed a week. Any infections resulting after pessary insertion will also be treated. When the pessary is placed, a sterile vaginal examination gel (non-antibiotic) will be used. Once the pessary is placed, patients will return to clinic every 2 weeks for an evaluation. A questionnaire will be filled out for symptoms, and a speculum exam performed to search for infections if the patient is symptomatic. Fetal biometry will be performed monthly, and a transvaginal cervical length will be measured every 2 weeks. The pessary will be removed if there are signs of tissue erosion of the cervix or vagina, intractable pain, or labor. Otherwise, the pessary is removed at 37 weeks.

The control arm will be followed with serial transvaginal ultrasounds to measure cervical length. If the length decreases to less than 20 mm, then vaginal progesterone 200 mg will be prescribed from a local pharmacy. If the cervical length continues to shorten such that membranes are visible at the os, then an emergent cerclage will be offered. Treatments will not be offered after 24 weeks gestation. Similar to the experimental group, patients will return to clinic every 2 weeks for an evaluation. A questionnaire will be filled out for symptoms, and a speculum exam performed to search for infections if the patient is symptomatic. Fetal biometry will be performed monthly, and a transvaginal cervical length will be measured every 2 weeks.

All patients enrolled in the study are seen at the high risk pregnancy clinic at the participating institutions for evaluation. The visit will be recorded in the electronic medical record. The visit will include prenatal care. Results are communicated back to the primary obstetrician by sending a copy of the clinic note back to the inbox of the primary obstetrician.

### **2.5.3 Allocation to treatment**

Patients will be assigned to their group based on a randomization scheme generated by a computer. Randomization is first stratified by location of the institution, then by random blocks within each institution. Once the assignment list is generated for each institution, the assignments are then placed in sealed, numbered, envelopes. The patients are assigned on a 1:1 basis between the two groups.

### **2.5.4 Treatment adherence**

Patients are asked to return to clinic at frequent intervals for an evaluation that includes history, transvaginal ultrasounds, and physical exam if needed. The pessary patients will return every 2 weeks after the pessary is placed. The control patients will have a weekly transvaginal ultrasound up to 24 weeks, then a clinic visit every 2 weeks.

### **2.5.5 Withdrawal of subjects due to non-compliance**

An intent-to-treat analysis will be used for analyzing study results. In the pessary group, if a patient removes the pessary, their outcomes will still be analyzed in the pessary group. In the control group, if patients do not use vaginal progesterone, their results are still analyzed in the control group. Patients who receive emergency cerclages are 100% compliant.

If patients do not return for their clinic visits or their delivery information is lost, their data cannot be analyzed. The investigators will call a minimum of 2 times, separated by a week, to ensure follow up. If unsuccessful, a letter will be mailed to the address of record requesting follow up. With regards to the primary outcome of preterm delivery, they will be assumed as having delivered the pregnancy at the gestational age they were lost to follow up.

### **2.5.6 Procedures to assess efficacy**

Patients are brought back to clinic for evaluation every 2 weeks. They will fill out a questionnaire reviewing their symptoms, fetal biometry will be performed, and the cervical length will be measured by transvaginal ultrasound. A physical exam (including a sterile speculum exam) will search for cervical and vaginal infections if patients are symptomatic. This information is recorded on the web-based case report form (CRF) built and stored by REDCap ([www.project-redcap.org](http://www.project-redcap.org)).

**2.5.7 Procedures to assess safety**

Patients are brought back to clinic for evaluation every 2 weeks. They will fill out a questionnaire reviewing their symptoms, fetal biometry will be performed, and the cervical length will be measured by transvaginal ultrasound. A physical exam (including a sterile speculum exam) will search for cervical and vaginal infections if patients are symptomatic. This information is recorded on the REDCap CRF.

**2.5.8 Schedule of study visits**

Schedule of Events for Pessary group <sup>+</sup>	Screening Visit	Study Visits									
	Visit 1, Day 0	Visit 2, Day 7*	Visit 3, Day 14	Visit 4, Day 28	Visit 5, Day 42	Visit 6, Day 56	Visit 7, day 70	Visit 8, Day 84	Visit 9, Day 98	Visit 10, Day 112	
Informed consent	X										
Medical history, demographics, and general health	X	X	X	X	X	X	X	X	X	X	
Review of current medications	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	X	X	
Fetal biometry	X			X		X		X		X	
TVCL	X	X	X	X	X	X	X	X	X	X	

+ assume enrollment at 20 weeks  
\* if needed

Schedule of Events for Non-Pessary group <sup>+</sup>	Screening Visit	Study Visits									
	Visit 1, Day 0	Visit 2, D 7*	Visit 3, D 14	Visit 4, D 21*	Visit 5, D 28	Visit 6, D 42	Visit 7, D 56	Visit 8, D 70	Visit 9, D 84	Visit 10 D 98	Visit 11, D 112
Informed consent	X										
Medical history, demographics, and general health	X	X	X	X	X	X	X	X	X	X	X
Review of current medications	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X
Fetal biometry	X				X		X		X		X
TVCL	X	X	X	X	X	X	X	X	X	X	X

+ assume enrollment at 20 weeks



\* if needed

## **2.6 Study outcome evaluations**

### **2.6.1 Study endpoints**

These are listed in sections 1.4.1 and 1.4.2. To repeat, the primary outcome is a preterm delivery less than 37 weeks 0 days.

### **2.6.2 Sample size determination**

Based on KUMC hospital data, the number of preterm births < 37 weeks 0 days gestation in patients with short cervixes (< 25 mm) is 30%. In order to detect a reduction in half to 15%, a sample size of 242 will be required to have power of 80% using a two-sided z-test assuming pooled variances. Level of significance is set at 0.05.

Based on records of patients currently treated for short cervixes here at KUMC over the past year, we experience about a 5% loss to follow up rate. Our sample size determination requires 242 subjects for analysis. We plan to enroll a total of 256 patients. We will use an intent-to-treat principle for analyzing the outcomes of the trial. All enrolled patients will provide informed consent for study participation.

### **2.6.3 Outcome data and data analysis**

When patients are admitted to the hospital for delivery of the fetus, the research team will record the information listed on the REDCap CRF. Both the mother and newborn hospital charts will be reviewed for the primary and secondary outcomes listed in sections 1.4.1 and 1.4.2. If patients deliver at another hospital, those records will be obtained with the patient's consent.

De-identified data from each institution will be stored on the REDCap website. That data will be downloaded into either Excel or SAS format for analysis. This file will be stored in the folder of Gene Lee MD, on the network server named "Sydney". This drive is password protected. Only members of the research team will be given access to the stored data.

The primary endpoint and the categorical outcomes that are part of the secondary endpoints will be reported using frequency counts and proportions. For the secondary endpoints that are continuous variables, summary statistics such as mean and standard deviation, or median and inter-quartile range will be reported based on whether the assumption of normality is justified. A chi-square test (or a Fisher's exact test) will be used to perform statistical comparison of proportions across the two groups. Likewise, comparisons for continuous outcomes will be done using a two-sample t-test (or Wilcoxon Rank Sum test) as will be deemed necessary. For gestational age, we will also compare the Kaplan Meier survival curves of the two groups (control and pessary) using the logrank test. Level of significance for all statistical tests will be set at 0.05.

As mentioned before, subjects lost to follow up will have the gestational age at delivery set at the point data was lost. An intent to treat analysis will then be performed. A sensitivity analysis will be conducted by omitting the incomplete data and recalculating the differences between the pessary and control groups. The changes in results will then be compared.

The Arabin pessary will be considered a success if the following conditions are met: 1) a statistically significant reduction of preterm birth is found in the group treated with the Arabin pessary, 2) the number of patients with incomplete data does not exceed 10%. If a statistically significant difference is observed, but missing data is equal or greater than 10%, then additional study with a larger sample size is warranted.

### **3.0 RISK ANALYSIS**

#### **3.1 Anticipated risks**

The primary physical risks of this study are

- 1) the pessary fails to reduce preterm birth
- 2) cervical amputation due to tight pessary constriction of the cervix
- 3) erosion of maternal tissue
- 4) maternal discomfort
- 5) vaginal infections
- 6) vaginal discharge, which may be mistaken for rupture of membranes
- 7) pain at insertion and/or removal
- 8) improper pessary placement

The risks are minimized by

- 1) This clinical trial is conducted after a large Spanish RCT suggested that the pessary is a better treatment than any current therapy. Rather than testing the pessary for the first time, our trial has the goal of confirming the prior Spanish results in a Midwest USA regional setting.
- 2) Patients are evaluated every 2 weeks for symptoms of pain, abnormal vaginal discharge, and infections. A questionnaire is completed, and a speculum exam to directly assess the cervical and vaginal tissue is performed as needed. Nitrazine, ferning, and pooling will be performed as needed to diagnosed rupture of membranes correctly. The pessary is removed if there are concerning signs of trauma, erosion, intractable pain, and bleeding. The NAMSA report reiterates the known safety of silicone pessaries (p8-9, 10-11).
- 3) Providers are taught how to insert and remove the pessary by instructional videos sponsored by Dr. Birgit Arabin, the inventor of the device. In addition, pain

experienced at insertion and/or removal will be treated with narcotic administration as needed.

Risk benefit analysis:

This study is conducted to confirm results of a larger RCT already concluded internationally. Those results strongly suggest that the pessary is more effective than any current therapy. These potential benefits outweigh the concerns for untreated short cervix with resulting preterm birth. The concern of tissue erosion is extremely low (please reference NAMSA report, p8-9, 10-11). These benefits accrue directly to the individual, and in aggregate, to society as a result.

### 3.2 Adverse event reporting

#### 3.2.1 Adverse event definitions

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

**Associated with the investigational device:** There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

**Life-threatening adverse effect:** Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

**Serious adverse effect:** An adverse effect is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- death
- a life-threatening AE
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect.

**Unanticipated adverse effect:** Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

#### 3.2.2 Eliciting adverse effect information

Clinical study subjects will be routinely questioned about adverse effects at study visits.

#### 3.2.3 Recording and assessment of adverse effects

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to

the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor-investigator.

#### **3.2.4 Abnormal test findings**

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study
- The test finding is considered an adverse effect by the sponsor-investigator

#### **3.2.5 Causality and severity assessment**

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

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

#### **3.2.6 Reporting adverse effects to the FDA**

For any observed or volunteered adverse event that is determined to be a UADE, the sponsor-investigator will submit an expedited safety report to the FDA's Center for Devices and Radiological Health. The expedited safety report will consist of:

- a completed [Form FDA 3500A](#)

- a cover letter analyzing the significance of the event

A copy of this safety report will be provided to all participating study investigators.

The completed [Form FDA 3500A](#) and cover letter will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If, following receipt and investigation of follow-up information regarding an adverse effect that was previously determined not to be a UADE, the sponsor-investigator determines that the event does meet the requirements for expedited reporting, the sponsor-investigator will submit a completed [Form FDA 3500A](#) and cover letter as soon as possible, but in no event later than 10 working days, after the determination is made.

Subsequent to the initial submission of a completed [FDA Form 3500A](#), the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

### **3.2.5 Reporting adverse effects to the responsible IRB**

For any adverse event determined to be a UADE, the sponsor-investigator will submit the completed [Form FDA 3500A](#) and cover letter to the IRB as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available.

### **3.3 Withdrawal of subjects due to adverse effects**

Patients are evaluated every 2 weeks for symptoms of pain, abnormal vaginal discharge, and infections. A questionnaire is completed, and a speculum exam to directly assess the cervical and vaginal tissue is performed as needed. Nitrazine, ferning, and pooling will be performed as needed to diagnosed rupture of membranes correctly. The pessary is removed if there are concerning signs of trauma, erosion, intractable pain, and bleeding.

Patients whose pessaries are removed are still analyzed in their assigned group according to an intent-to-treat analysis. Their outcomes and complications are recorded similar to other subjects. They are not replaced.

## **4.0 DESCRIPTION OF THE INVESTIGATIONAL DEVICE**

Please see NAMSA report for description of cytotoxicity, sensitization, irritation, acute systemic toxicity, subchronic systemic toxicity, genotoxicity, implantation, chronic systemic toxicity in detail.

In this study, the Arabin pessary will be for single patient use only. Each enrolled patient will be given their own new pessary. The patient will use the same pessary throughout the length of the study.

Please see MEDCERT certificates for information regarding manufacturing, quality management, and distribution. Pessaries are stored at room temperature and do not require special packaging. The principal investigators “install” the pessaries after they are appropriately trained by a video tutorial.

The following description is *modified* from <http://www.dr-arabin.de/e/cerclage/html>

The Arabin pessary is a ring manufactured from medical grade silicone. It has outer and inner diameters that vary, a height when laid flat, and a curvature to one side of the pessary. The width of the outer and inner diameters are chosen depending on the individual constitution of the pregnancy patient. The curvature of the pessary is upwards so that the pelvic floor supports the larger diameter. The smaller, inner diameter encompasses the cervix. After application the pessary changes the inclination of the cervical canal, directing it more posteriorly (figure 1). Thus the weight of the pregnancy is more on the anterior lower segment, as can be observed by TVS in selected cases. The use of a spreading gliding compound facilitates pessary insertion. The silicone material is inert and does not react with the vaginal epithelium or cervical epithelium. The silicone pessary does not change during its placement in the vaginal canal. In general, singleton pregnancies require a pessary height of 21-25 mm, and multiple pregnancies require a pessary height of 25-30 mm.

There are 13 sizes of the Arabin cervical pessary, differing by their outer diameter, inner diameter, and height. The investigators will be appropriately trained according to instructional videos. If insufficient, there are provision plans to be trained in person by the manufacturer. The pessary size will be selected based on a best fit to the patient’s anatomy. This proper fit will help obviate the risk of cervical amputation.

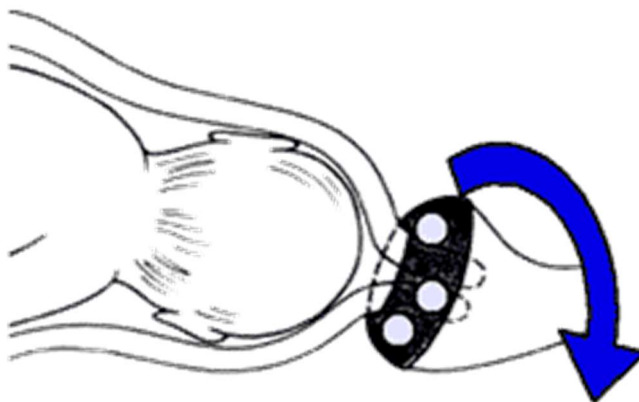


Figure 1

## 5.0 MONITORING PROCEDURES

Independent monitoring of the study for compliance with the clinical protocol and with IDE regulations will be conducted periodically by qualified staff of the University of Kansas Medical Center. The data from both sites will be reviewed every 6 months by the designated medical monitor for the study, Vishal Pandey MD. Dr. Pandey will not be blinded as he is searching for adverse events occurring in the pessary group. In addition, Gene Lee MD and John Moore RN, a research coordinator assigned to the study, will conduct monthly chart audits at KUMC to compare clinic, hospital, and research records for accuracy of data entry. Eugene Chang MD will conduct monthly chart audits at MUSC. If an adverse event is encountered, reporting to the Human Subjects Committee (HSC) at KUMC and the FDA will occur as detailed in section 3.2. Principal investigators who are notified of possible adverse events will also proceed as detailed in section 3.2.

Medical Monitor Contact Information:

Vishal Pandey, MD

Neonatologist

University of Kansas Medical Center

3901 Rainbow Boulevard

Kansas City, KS 66160

Phone: 913-588-6337

Email: [vpandey@kumc.edu](mailto:vpandey@kumc.edu)

Fax: 913-588-6317

The medical monitor is specifically chosen outside of the department of OBGYN to allow for objectivity.

Adverse events which would require immediate suspension of study for review would include an excess of 1 maternal death, 1 maternal ICU admission for sepsis, or 2 perinatal deaths in the **pessary** group.

Unanticipated adverse events will be reported immediately to the HSC, and its recommendations for temporary cessation or continuation of the study will be followed. If an excess of 4 perinatal deaths occur in the **pessary** group, the study should be concluded.

## 6.0 LABELING

The investigators will attach a label to the outside of the package containing the pessary.

The labeling will contain the statement "CAUTION - Investigational Device. Limited by Federal (or United States) Law to Investigational Use. This device is for single patient use only" [§ 812.5(a)].

Copies of the labels are provided in this submission. Refer to label for more information.

## **7.0 INFORMED CONSENT**

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor-Investigator will prepare the informed consent form and provide the documents to IRB for approval. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Sponsor-Investigator will retain an IRB-approved copy of the Informed Consent Form in the study master file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

## **8.0 IRB INFORMATION**

The study will be submitted and reviewed by the Human Subjects Committee (IRB) at the University of Kansas Medical Center and Medical University of South Carolina prior to starting any study activities. UADEs will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Sponsor-Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, device information, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.



## 9.0 ADDITIONAL RECORDS AND REPORTS

### 9.1 Data handling and record-keeping

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

*Source Data* are the clinical findings and observations, laboratory and test data, and other information contained in *Source Documents*. *Source Documents* are the original records (and certified copies of original records); including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, etc. When applicable, information recorded on the CRF shall match the *Source Data* recorded on the *Source Documents*.

Case reports forms were created using REDCap. REDCap is a secure, web-based application for building and managing online surveys and databases. Data will be entered and maintained in the REDCap system. Access to the system will be limited to only persons on the study team that are involved in the collection and management of study data.

### 9.2 Record maintenance and retention

The sponsor-investigator will maintain records in accordance with 21 CFR 812, Subpart G, to include:

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted Form FDA 3500A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators
- Curriculum vitae (sponsor-investigator and clinical protocol sub-investigators)
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor-investigator and listed sub-investigators
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Laboratory certification information

- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Master randomization list
- Signed informed consent forms
- Completed Case Report Forms, signed and dated by sponsor-investigator
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of sponsor-investigator correspondence to sub-investigators, including notifications of adverse effect information
- Subject screening and enrollment logs
- Subject identification code list
- Investigational device accountability records, including documentation of device disposal
- Interim data analysis report(s)
- Final clinical study report.

The sponsor-investigator will retain the specified records and reports for up to two years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational device, until two years after investigations under the IDE have been discontinued and the FDA so notified.

#### 10.0 Addition or removal of investigators

Any investigators added to the protocol must sign the investigator agreement prior to inclusion as a member of the study team. Investigators can be removed from the study team as needed.