Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAQ0916(M00Y05)	**Protocol Status:**	Approved
Effective Date:	11/13/2019	**Expiration Date:**	11/12/2020
Originating Department Code:		ANE Anesthesiology (751000X)	
Principal Investigator:		Smiley, Richard (rms7)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Chloroprocaine versus bupivacaine spinal anesthesia for cervical cerclage		
Protocol Version #:	1	**Abbreviated Title:**	Chloroprocaine for cerclage
Was this protocol previously assigned a number by an IRB:		No	

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?
No

Renewal Information

Enrollment status:
Open to enrollment or ongoing review of records/specimens
Provide any additional information necessary to explain the study status:
We have added the clinicaltrials.gov number--should have been added before
Since the last renewal:
Have there been any changes in the relevant literature that would affect the study design or procedures?
No
Have there been any interim findings associated with this study?
No
Have there been any publications resulting from this study?
No
Have any participants been enrolled using the Short Form process?
No
Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?
No
Is an annual Progress Report required by the funding organization or coordinating center for this study?
No
Does this submission include a modification?
Yes

Provide a description of, and explanation for, all changes being proposed in this submission:
change in personnel. Feloows Zheng and Shatil have left Columbia. New Fellows Bernstein and Daoud are added to protocol, Of note, we continue to be told that Dr. Bernstein does not have the "FDA part" of her RASCAL exams when we add her to IRB protocols, but we have repeatedly sent her certificate to the IRB--not sure what the problem is

Indicate which sections of the Rascal submission are affected by the proposed modification. Each marked section must be revised as part of this submission:

[ ]General Information
[ ]Attributes
[ ]Exempt and Expedited
[x]Personnel

[ ]Funding
[ ]Research Aims and Abstracts
[ ]Locations
[ ]Data Security and Privacy
[ ]Informed Consent/Recruitment
[ ]No revisions to submission content required
[ ]Background
[ ]Procedures
[ ]Subjects
[ ]Risks/Benefits/Monitoring
[ ]Attachments (including Rascal-generated attachments)

Has the consent form been revised in this submission?

No

Does this submission include a report of a protocol violation?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)
[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)
[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

No

Please indicate if any of the following University resources are utilized:

[ ] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)
[ ] CTSA-Irving Institute Clinical Research Resource (CRR)
[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)
[x] None of the above

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Cervical insufficiency, defined as the inability of the uterine cervix to retain a pregnancy in the second trimester, in the absence of uterine contractions,[1] affects 1% of the obstetric population (about 1 in 500 pregnancies)[2] and 8% of populations with recurrent miscarriages and mid-trimester pregnancy losses.[3] Cervical cerclage is a surgical procedure performed via the vaginal route, whereby a suture is inserted at the junction of vagina and cervix, at the level of the internal os of the cervix, to provide mechanical support and prevent preterm birth. The procedure is usually performed as an elective outpatient procedure with a duration of approximately 30 minutes, but occasionally is performed as an emergency, in the case of threatened miscarriage. An anesthetic technique with a relatively short duration of action and recovery is indicated. Both regional and general anesthesia have been successfully used;[2] however spinal anesthesia is now overwhelmingly the choice, as it has the advantage of preserving maternal airway reflexes and limiting fetal exposure to anesthetic agents (although the procedure is usually performed beyond the stage of highest teratogenicity risk). Throughout most of the 1990s, lidocaine was the intrathecal local anesthetic agent of choice for these procedures, but fell out of favor because of the frequency of reports of transient neurologic symptoms (TNS)- the reported incidence ranges from 10 – 40%.[4-6] Patients with TNS experience cramping, aching, or lancinating pain affecting the lower extremities and buttocks. Symptoms, which may have variable severity, occur within 6 - 36 hours after spinal anesthesia and last between 1 – 7 days. Bupivacaine is now the most common local anesthetic used for this procedure. Bupivacaine is associated with far less TNS but is a long-acting agent and carries the disadvantage of a prolonged anesthetic recovery, which is a source of significant patient dissatisfaction and impacts staffing and resources due to unnecessarily long post-anesthesia care unit (PACU) stays. In our practice at CUMC, with typical dosing of intrathecal hyperbaric bupivacaine 0.75% ranging from 7.5 – 9 mg, usually in conjunction with fentanyl 10 – 20 mcg, patients sometimes spend 5 hours or more in the PACU after a 30-minute outpatient cervical cerclage procedure. These prolonged stays are partly a consequence of the CUMC practice that maintains that patients must be able to void and ambulate independently prior to discharge home, due to concerns about the risk of falls and readmission for urinary retention. Chloroprocaine (2-chloroprocaine, CP) is an amino-ester local anesthetic with a fast onset and short duration that has made a resurgence for use in spinal anesthesia for ambulatory procedures.[7] Although safe reports of its use for spinal anesthesia were published following its introduction in 1952,[8] CP was never widely adopted, probably due to the availability of lidocaine, which had been introduced in 1949. The drug has had widespread use for epidural anesthesia, and due to its rapid onset and low systemic toxicity, is considered to be critical for the safe practice of obstetric anesthesiology (including at CUMC) for use in emergencies such as “stat” cesarean sections in women with epidural catheters in place for labor anlagesia. Serious concerns about the safety of the use of CP intrathecally arose in the wake of a series of case reports in the 1980’s of catastrophic neurologic sequelae, such as adhesive arachnoiditis, following the injection of large doses of the drug (average 611 mg) that had been meant to be injected into the epidural space.[9-11] Neurotoxicity was attributed to the preservative sodium bisulphite, which was hypothesized to

provoke the release of sulphur dioxide, in the presence of the low pH of CP. Animal studies have been inconclusive, with conflicting results believed to be related to interspecies variation in levels of sulfur oxidase (catalyzes sulfites to sulfates), although variable results have also been seen in studies involving the same species.[12] The current formulation of CP has no additives. Vaghadia *et al.*[13] performed a recent trial involving 40 patients randomized to undergo transurethral resection of the prostate with spinal anesthesia with either preservative free CP or lidocaine. Several patients in the lidocaine group experienced TNS, and notably one patient in the CP group developed an incomplete cauda equina syndrome that developed 24 hours later and persisted for several weeks. The cause of that unfortunate complication is unclear. Contemporary reports of use spinal CP began to reappear in small studies in volunteers in the mid-2000's and then larger studies followed, investigating its properties, such as minimum effective dose, and behavior with added dextrose and clonidine, as well as comparisons with bupivacaine and lidocaine.[14-26] This work supports the safety of the use of spinal CP, demonstrates the low incidence of TNS and particular suitability for surgeries in an ambulatory practice setting. CP is currently used very frequently at CUMC for spinal anesthesia for ambulatory surgical patients, especially for lower extremity orthopedic procedures such as knee arthroscopy. A CUMC Anesthesiology Department review of CUMC practice between 2009 – 2014 reported 412 cases of CP use for spinal anesthesia, with no associated complications. [27] A randomized controlled trial of spinal anesthesia with bupivacaine or 2-chloroprocaine during cesarean section was recently published; the authors reported no difference in time to motor block resolution among groups, but a more predictable recovery was noted with 2-chloroprocaine.[28] There are no published reports of the use of CP for spinal anesthesia for cervical cerclage or other outpatient procedures in obstetric population. We plan to perform a study in which patients undergoing cervical cerclage with spinal anesthesia will be randomized to receive either plain 3% 2-chloroprocaine 50 mg or hyperbaric bupivacaine 9mg in conjunction with 15 mcg fentanyl. Our hypothesis is that the use of CP for outpatient spinal anesthesia for cervical cerclage will lead to faster recovery of motor and sensory function than bupivacaine spinal anesthesia, which is currently the customary practice at CUMC. Between 5 - 10 cervical cerclage procedures are performed each month on the CHONY labor and delivery floor. We believe CP spinal anesthesia, compared with the bupivacaine spinal anesthesia, will result in higher patient and higher staff satisfaction, and potentially economic benefits associated with earlier PACU discharge and decreased nursing staff workload. **References:**

1. ACOG Practice Bulletin No.142: Cerclage for the management of cervical insufficiency. Obstetrics and gynecology 2014;123:372-9.
2. Ioscovich A, Popov A, Gimelfarb Y, et al. Anesthetic management of prophylactic cervical cerclage: a retrospective multicenter cohort study. Archives of gynecology and obstetrics 2015;291:509-12.
3. Alfirevic Z, Stampalija T, Roberts D, Jorgensen AL. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. The Cochrane database of systematic reviews 2012;4:CD008991.
4. Schneider M, Ettlin T, Kaufmann M, et al. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. Anesthesia and analgesia 1993;76:1154-7.
5. Tarkkila P, Huhtala J, Tuominen M. Transient radicular irritation after spinal anaesthesia with hyperbaric 5% lignocaine. British journal of anaesthesia 1995;74:328-9.
6. Freedman JM, Li DK, Drasner K, Jaskela MC, Larsen B, Wi S. Transient neurologic symptoms after spinal anesthesia: an epidemiologic study of 1,863 patients. Anesthesiology 1998;89:633-41.
7. Goldblum E, Atchabahian A. The use of 2-chloroprocaine for spinal anaesthesia. Acta anaesthesiologica Scandinavica 2013;57:545-52.
8. Foldes FF, Mc NP. 2-Chloroprocaine: a new local anesthetic agent. Anesthesiology

1952;13:287-96.9. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesthesia and analgesia 1980;59:452-4.10. Ravindran RS, Turner MS, Muller J. Neurologic effects of subarachnoid administration of 2-chloroprocaine-CE, bupivacaine, and low pH normal saline in dogs. Anesthesia and analgesia 1982;61:279-83.11. Moore DC, Spierdijk J, vanKleef JD, Coleman RL, Love GF. Chloroprocaine neurotoxicity: four additional cases. Anesthesia and analgesia 1982;61:155-9. 12. Pollock JE. Intrathecal chloroprocaine--not yet "safe" by US FDA parameters. International anesthesiology clinics 2012;50:93-100.13. Vaghadia H, Neilson G, Lennox PH. Selective spinal anesthesia for outpatient transurethral prostatectomy (TURP): randomized controlled comparison of chloroprocaine with lidocaine. Acta anaesthesiologica Scandinavica 2012;56:217-23.14. Kouri ME, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with lidocaine in volunteers. Anesthesia and analgesia 2004;98:75-80, table of contents.15. Warren DT, Kopacz DJ. Spinal 2-chloroprocaine: the effect of added dextrose. Anesthesia and analgesia 2004;98:95-101, table of contents.16. Vath JS, Kopacz DJ. Spinal 2-chloroprocaine: the effect of added fentanyl. Anesthesia and analgesia 2004;98:89-94, table of contents.17. Smith KN, Kopacz DJ, McDonald SB. Spinal 2-chloroprocaine: a dose-ranging study and the effect of added epinephrine. Anesthesia and analgesia 2004;98:81-8, table of contents.18. Davis BR, Kopacz DJ. Spinal 2-chloroprocaine: the effect of added clonidine. Anesthesia and analgesia 2005;100:559-65.19. Gonter AF, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with procaine in volunteers. Anesthesia and analgesia 2005;100:573-9.20. Kopacz DJ. Spinal 2-chloroprocaine: minimum effective dose. Regional anesthesia and pain medicine 2005;30:36-42.21. Casati A, Danelli G, Berti M, et al. Intrathecal 2-chloroprocaine for lower limb outpatient surgery: a prospective, randomized, double-blind, clinical evaluation. Anesthesia and analgesia 2006;103:234-8, table of contents.22. Casati A, Fanelli G, Danelli G, et al. Spinal anesthesia with lidocaine or preservative-free 2-chlorprocaine for outpatient knee arthroscopy: a prospective, randomized, double-blind comparison. Anesthesia and analgesia 2007;104:959-64.23. Camponovo C, Wulf H, Ghisi D, et al. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: a prospective, observer-blinded, randomised, controlled trial. Acta anaesthesiologica Scandinavica 2014;58:560-6.24. Yoos JR, Kopacz DJ. Spinal 2-chloroprocaine for surgery: an initial 10-month experience. Anesthesia and analgesia 2005;100:553-8.25. Yoos JR, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with small-dose bupivacaine in volunteers. Anesthesia and analgesia 2005;100:566-72.26. Hejtmanek MR, Pollock JE. Chloroprocaine for spinal anesthesia: a retrospective analysis. Acta anaesthesiologica Scandinavica 2011;55:267-72. 27. Ivie R, Fu P, Maniker R. Chloroprocaine Spinal Compared to General Anesthesia for Outpatient Knee Arthroscopy. 40th Annual Regional Anesthesiology and Acute Pain Meeting. Las Vegas, Nevada 2015.28. Maes S, Laubach M, Poelaert J. Randomised controlled trial of spinal anaesthesia with bupivacaine or 2-chloroprocaine during caesarean section. Acta anaesthesiologica Scandinavica 2015; Nov 26. [Epub ahead of print]

Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

This will be a prospective, randomized, double blind clinical trial. Subjects will be ASA I and II women 18 yrs old with singleton pregnancy in the 1st or 2nd trimester of pregnancy undergoing cervical cerclage with spinal anesthesia. Patients will be randomly allocated to the chloroprocaine (CP) or bupivacaine group (BUP). Patients will receive spinal anesthesia with either chloroprocaine 50 mg with fentanyl 15 mcg or bupivacaine 9 mg with fentanyl 15 mcg. The onset and resolution of sensory and motor blockade, and time to achieve PACU discharge criteria, as well as patient comfort and satisfaction with the procedure will be closely evaluated. The following day, patients will be telephoned by an investigator to inquire about their satisfaction with their anesthesia and the incidence of TNS symptoms, back pain and postdural puncture headache.

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The null hypothesis is that there is no difference in recovery of sensory and motor function between CP 50 mg + fentanyl 15 mcg and bupivacaine 9mg + fentanyl 15 mcg. Our primary outcome will be mean time from spinal injection (tIT) to time to no motor block (t motor) (i.e. (t IT- t motor), which corresponds to PACU discharge readiness. Previous studies of outpatient surgical procedures suggest that this time is 200 - 300 minutes (SD ~ 50 min) with bupivacaine, 150 - 200 minutes with lidocaine and 150 minutes with CP, with standard deviations (when reported) averaging about 10 - 20% of the values.[References: 1, 2, 3]

We will consider a difference between groups of 45 minutes to be clinically significant. Secondary outcomes will include the time from intrathecal injection to time to ambulate (tIT - t amb) and void (tIT - t void) (CUMC discharge criteria), rating of intraoperative discomfort, and incidence of TNS. To reliably detect a 45 minute difference with a 25% standard deviation (e.g., 225 +/- 56.25 versus 180 +/- 45 minutes) with 80% power and an alpha of 0.05 will require 21 subjects per group. We will recruit 25 per group to account for dropouts (expected to be low) and the possibility of non-normal data. In reality, we expect a greater difference than 45 minutes between groups, and believe the study is well-powered to find a clinically significant difference.

References:

1. Camponovo C, Wulf H, Ghisi D, et al. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: a prospective, observer-blinded, randomised, controlled trial. Acta anaesthesiologica Scandinavica 2014;58:560-6.

2. Hejtmanek MR, Pollock JE. Chloroprocaine for spinal anesthesia: a retrospective analysis. Acta anaesthesiologica Scandinavica 2011;55:267-72.

3. Yazicioglu D, Akkaya T, Kulacoglu H. Addition of lidocaine to bupivacaine for spinal anaesthesia compared with bupivacaine spinal anaesthesia and local infiltration anaesthesia. Acta anaesthesiologica Scandinavica 2013;57:1313-20.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):
No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?
No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?
No

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Columbia/CUMC	MSCHONY 10				

Personnel

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
rms7 212-305-5006	Smiley, Richard	Principal Investigator	ANE Clinical Operations (751030X)	Edit	Y
	Roles and Experience: Chief Division of Obstetric Anesthesia				
al3196 305-582-6077	Lee, Allison	Investigator	ANE Clinical Operations (751030X)	Edit	Y
	Roles and Experience: Co-investigator				
bd2369 631-745-0180	Daoud, Bahaa	Investigator	ANE Education (751040X)	Edit	Y
	Roles and Experience: Obstetric Anesthesia Fellow				
br2469 212-305-3917	Raposo Corradini, Beatriz	Investigator	ANE Research Operations (751050X)	View	Y
	Roles and Experience: Research coordinator				
krb2115 917-575-5153	Bernstein, Kyra	Investigator	ANE Education (751040X)	Edit	Y
	Roles and Experience: Obstetric Anesthesia Fellow				
rl262 212-342-2028	Landau-Cahana, Ruth	Investigator	ANE Clinical Operations (751030X)	View	Y
	Roles and Experience: Co-investigator				

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	GCP - Third-party tracking	GCP Refresher	Genetic Research Consent
rms7	Smiley, Richard	03/12/2019	11/18/2003	07/27/2019	09/25/2016	09/25/2016			10/24/2019			
al3196	Lee, Allison	02/25/2019	10/08/2012	06/02/2018	06/02/2018	06/02/2018						
bd2369	Daoud, Bahaa	03/30/2019	04/05/2018	04/06/2018		08/20/2019			04/05/2018			
br2469	Raposo Corradini, Beatriz	09/23/2019	12/09/2014	12/12/2017	12/23/2014	12/23/2014		12/11/2014	12/12/2017			
krb2115	Bernstein, Kyra	10/24/2019	06/13/2011	04/15/2019			08/20/2019		04/17/2019			
rl262	Landau-Cahana, Ruth	09/26/2019	09/26/2014	10/27/2017	10/27/2014	10/27/2014			03/29/2018			

Departmental Approvers

Electronic Signature: Bahaa Daoud (751040X) - Investigator Date: 10/16/2019

Electronic Signature: Richard Smiley (751030X) - Principal Investigator Date: 10/11/2019

Electronic Signature: Frances Antonetty (751050X) - Department Administrator Date: 10/14/2019

Electronic Signature: Kyra Bernstein (751040X) - Investigator Date: 10/15/2019

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[x]Hardcopy (i.e., paper)

Describe where and how the data will be stored:

During the study period, any hard copy data collection materials will be stored in a secure cupboard in a locked office on the CHONY Tower 10th floor, Room #1048. Following this period, once patient assessments have concluded, the cover sheet of the data collection instrument, indicating the patient name and ID number will be safely discarded and only de-identified hard copy (i.e, paper) data will be saved. No sensitive data will be saved. Only de-identified data which does not contain sensitive information will be entered into a secure, encrypted web site, RedCap, supported by CUMC.

[x]Electronic

Where will the data be stored?

Y
[x]On a System
[ ]On an Endpoint

Does this study involve the receipt or collection of Sensitive Data?
Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:
[ ]Personally Identifiable Information (PII), including Social Security Numbers (SSN)
Will Social Security Numbers (SSNs) be collected for any purpose?
[x]Protected Health Information (PHI), including a Limited Data Set (LDS)
If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply
[x]Sensitive data will not be stored in electronic format
[ ]Sensitive data will be stored on a multi-user system
[ ]Sensitive data will be stored on an encrypted endpoint

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):
During the study period of approximately 24 hours, any data collection materials will be stored in a secure cupboard in a locked office on the CHONY Tower 10th floor, Room #1048. Following this period, once patient assessments have concluded, the cover sheet of the data collection instrument, indicating the patient name and ID number will be safely discarded and only de-identified data will be saved and discussed with investigators at this and other sites.
No sensitive data or PHI will be stored or shared electronically. De-indentified data will be stored using the CUMC supported database system, RedCap, the data for which is stored on secure, encrypted servers.

The following individuals and/or agencies will be able to look at and copy research records:
The investigator, study staff and other medical professionals who may be evaluating the study; -Authorities from Columbia University and New
York-Presbyterian Hospital, including the Institutional Review Board ('IRB'); -External, exclusive contractors who may be reviewing compliance with research policies; -The Office of Human Research Protections ('OHRP')

If your project is not NIH funded, has a Certificate of Confidentiality (CoC) been requested for this research?
No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:
During the study period of approximately 24 hours, any data collection materials will be stored in a secure cupboard in a locked office on the CHONY Tower 10th floor, Room #1048.

Procedures

Is this project a clinical trial?

Yes

Is this project a clinical trial that requires registration with www.clinicaltrials.gov?

Yes

Has this study been registered with www.clinicaltrials.gov?

No

Please note that this section should be updated when the registration number is received. At this time, please indicate who will be responsible for registering the study:

NCT02862912

Is this project associated with, or an extension of, an existing Rascal protocol?

No

Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review

No

Audio and/or video recording of research subjects

No

Behavioral Intervention?

No

Biological specimens (collection or use of)

No

Cancer-related research

No

Drugs or Biologics

Yes

Future use of data and/or specimens

No

Genetic research

No

Human embryos or human embryonic stem cells

No

Imaging procedures or radiation

No

Medical Devices

No

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

No

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

No

Educational testing

No

Non-invasive physical measurements

Yes

Taste testing

Yes

Is there an external protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

This will be a prospective, randomized, double blind clinical trial. Subjects will be ASA I and II women 18 yrs with singleton pregnancy in the 1st or 2nd trimester of pregnancy undergoing cervical cerclage with spinal anesthesia. Maternal height will be between 150 – 180 cm and the body mass index (BMI) 40 kg/m2. A member of the investigation team will approach patients to discuss the study and obtain written informed consent following the preoperative assessment and consent for anesthesia care for cervical cerclage.

After enrollment, each patient will be randomly allocated to the chloroprocaine (CP) or bupivacaine group (BUP) by opening an opaque envelope with the assignment (CP) or (BUP). The randomization table will be created with block randomization in blocks of 10. The proportion for the treatment and placebo groups will be 1:1. The investigator opening the envelope will prepare the drug and provide it in a sterile fashion for the investigator who will administer the drug, without revealing the group allocation

Exclusion criteria will include any contraindication to neuraxial anesthesia, history of neurologic disease, including multiple sclerosis, spinal stenosis, central or peripheral neuropathies, pre-existing/chronic back pain, ester local anesthetic allergy, PABA allergy, or history of atypical cholinesterase (CP is metabolized by cholinesterase).

While receiving co-hydration with lactated Ringer's solution 500 ml, patients will undergo spinal anesthesia at the L3-4 or L4-5 interspace with a midline approach, using a 25 G Whitacre spinal needle. Patients will be in the sitting or lateral decubitus position, depending on the discretion of attending anesthesiologist.

Patients allocated to group CP will receive: 3% 2-chloroprocaine 50 mg (NesacaineR , Fresenius Kabi USA, LLC. Lake Zurich) (1.67 ml) and fentanyl 15 mcg (0.3 ml).

Patients in the BUP group will receive hyperbaric 0.75% bupivacaine 9 mg (1.2 ml), with fentanyl 15 g (0.3 ml), with saline (0.5 ml) to bring the volume to ~ 2 ml)

Immediately following intrathecal injection, the patient will be laid supine. The patient, the anesthesiologist performing the injection and all persons making subsequent observations will be blinded to the group allocation.

Sensory level to pinprick will be performed q 2 min until a constant sensory level has been achieved for 2 consecutive tests. Motor block will also be assessed q 2 min using the Bromage scale:

Bromage Scale

I = free movement of the legs and feet = no block

II = able to flex knees, with free movement of feet = partial (33%) block

III = unable to flex knees, but with free movement of the feet = almost complete (66%) block

IV = unable to move legs or feet = complete block (100%)

Once a T12 sensory level to pinprick has been achieved, and after spending at least 3 min in the supine position, the patient's legs will be placed in stirrups bilaterally (lithotomy position). Success of the block will be considered to be T12 or higher. Inability to reach T12 within 20 min of injection will be considered a block failure.

Patient subjective intraoperative pain scores will be assessed according to a verbal rating scale (VRS) from 0 – 10, where 0 = no pain and 10 = worst imaginable pain, at surgery start (placement of the speculum) and at the time of clamp of the cervix.

Intraoperative complaints of pain (VRS > 4) will be treated with fentanyl 50 mcg iv q 5 min x 2 doses, prn. The anesthetic will be considered a failure (operation) for either failure to achieve T12 sensory level to pinprick, or failure to achieve a pain score of VRS 2 intraoperatively, despite 2 doses of fentanyl 50 mcg iv.

Any additional need for supplemental analgesics or anxiolysis, including the need to convert to general anesthesia, will be at the discretion of the anesthesia attending.
In case of failure (induction) or failure (operation), conversion to another anesthetic technique and choice of technique will be at the discretion of the attending anesthesiologist.

Data recorded:

Times:
•End spinal injection (t -IT)
•Anesthesia ready (sensory level T12 or higher) - (t -ready)
•Time surgery start - placement of speculum (t-start)
•Time cervix clamped (t- Cx)
•Time surgery end (t-End)
•Time of resolution sensory blockade (t- sensory)
•Time of motor block resolution –using Bromage score (t- motor)
•Time of ambulation unassisted (t-amb)
•Time able to void (t-urine)

Other data to be recorded will be NPO time, preoperative and intraoperative fluid administration, intraoperative nausea/vomiting and pruritus (none, mild, moderate, severe). The BP will be measured q 1 min for the first 5 min and then q 3 – 5 min. Use of vasopressors intraoperatively will be recorded. We will record the need for supplemental iv analgesia, anxiolytics, local anesthesia injection by the obstetrician. Perioperative administration of NSAIDs, and obstetric complications such as vaginal bleeding, uterine contractions, abdominal pain will be documented.

Postoperatively, the sensory level to pinprick and motor block will be assessed by an investigator in the PACU, at q 15-min intervals for the first hour and then q 30 min until discharge. Patients will be asked about subjective pain using a VRS from 0 – 10, where 0 = no pain and 10 = worst imaginable pain. At one hour, symptoms of nausea and pruritus will be rated as none, mild, moderate, or severe. Postoperative (PACU) administration of supplemental analgesics or treatment for pruritus or nausea, will be recorded.

The next day, between 18 - 30 hours postoperatively, the patient will be telephoned for follow-up by an investigator who is blinded to the patient's group allocation. The patient will be asked to rate their satisfaction with the anesthetic for the procedure (complete, adequate or inadequate), symptoms of TNS (pain or abnormal sensations including

hypoesthesia or dysesthesias in the gluteal region, radiating to the lower extremities). The patient will be asked to rate the severity of those symptoms using a VRS from 0 – 10, where 0 = no pain and 10 = worst imaginable pain. She will similarly be asked about back pain, headache and her use of post-operative analgesics. Patients with significant symptoms of TNS, headache or other complication will be asked to return to CUMC for evaluation and management. If any concerns or complications occur at any point during the study period, unblinding will occur and the principal investigator will be notified immediately.

The primary outcome will be the mean difference between groups in time between the end of spinal injection (t IT) to time for no motor block (t motor), i.e. tIT - T motor. Secondary outcomes will include the time to ambulate and void (CUMC discharge criteria), rating of intraoperative discomfort, side effects and incidence of TNS.

Drugs/Biologics

On the General Information page you have indicated that the protocol version associated with the use of this drug/biologic is as follows: 1

Please note that a Protocol Version # is required for protocols using a drug or biologic, and you will not be allowed to submit this protocol until the Protocol Version # field is complete. Please ensure that the Protocol Version # is completely and accurately reported on the General Information page.

List each drug or biologic that will be administered as the object of the protocol or is being used because it is relevant to the aims of the research protocol. This applies whether the drug/biologic is not yet FDA-approved (i.e., is investigational), is FDA approved and used in accordance with its labeling, or is an approved product that is being used in an investigational manner (i.e., off-label use is being studied).

Note that the questions apply only to drugs used in clinical investigations. Emergency use of a drug that is not yet FDA-approved is not a clinical investigation, and a submission in Rascal may not be required. Please contact the IRB for assistance if emergency use of a drug or biologic that is not yet FDA-approved is being considered: (212) 305-5883.

Name:
Bupivacaine HCl 0.75% in Dextrose 8.25% Injection
Dose:
9 mg
Study phase:
Phase 4
Manufacturer Information

Name:	Hospira, Inc.
Address:	Lake Forest, IL 60045 USA
Contact information:	(224) 212-2000

Route of administration:
Intrathecal
Is the drug/biologic FDA-approved and used in accordance with its labeling?
Yes

An IND/BB-IND is not required. A copy of the package insert must be attached.

Name:

Chloroprocaine

Dose:

50 mg

Study phase:

Phase 4

Manufacturer Information

Name:	APP Fresenius Kabi, USA LLC
Address:	Three Corporate Drive Lake Zurich, Illinois 60047
Contact information:	Main Phone (847) 550-2300

Route of administration:

Intrathecal

Is the drug/biologic FDA-approved and used in accordance with its labeling?

No

Select a category:

FDA-approved but not used in accordance with the currently approved labeling

Does the Use of the drug/biologic require an Investigational New Drug (IND) or Biological IND (BB-IND) application?

NO – this use is exempt.

Since you have indicated that the drug/biologic is either FDA approved but being used outside of its approved indication, or not FDA-approved, an IND is required unless the clinical investigation meets criteria to be exempt from the IND requirements. Please choose the regulatory category for exemption from the IND requirements that applies to your study.

21 CFR 312.2(b)(1) criteria met - This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following apply: (i)The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; and (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following apply:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

Will the drug/biologic be dispensed by the CUMC Research Pharmacy, which is responsible for the storage, handling, accountability, and dispensing of investigational drugs to research investigators? CUMC Research Pharmacy policy: https://researchpharmacy.cumc.columbia.edu/policies.html

No, the drug will not be dispensed by the Research Pharmacy

Please explain:

This drug is already used frequently and safely for epidural and spinal injection at CUMC and around the world, despite the FDA labeling. It is not necessary that it be dispensed by the Research Pharmacy as the drug is already in use at CUMC and used in the same manner in which it will be administered during this study. Furthermore, since the drug is unstable to light, it must be drawn up immediately before administration. It would actually be less safe for the drug to be prepared by the Research Pharmacy and subsequently transferred to investigators. The most appropriate method of preparation would be drawing up the drug in a sterile fashion by the clinician actually performing spinal anesthesia at the time of the procedure.

Name:

Fentanyl

Dose:

15 mcg

Study phase:

Phase 4

Manufacturer Information

Name:	Hospira, Inc,
Address:	275 N Field Dr, Lake Forest, IL 60045
Contact information:	(224) 212-2000

Route of administration:

Intrathecal

Is the drug/biologic FDA-approved and used in accordance with its labeling?

No

Select a category:

FDA-approved but not used in accordance with the currently approved labeling

Does the Use of the drug/biologic require an Investigational New Drug (IND) or Biological IND (BB-IND) application?

NO – this use is exempt.

Since you have indicated that the drug/biologic is either FDA approved but being used outside of its approved indication, or not FDA-approved, an IND is required unless the clinical investigation meets criteria to be exempt from the IND requirements. Please choose the regulatory category for exemption from the IND requirements that applies to your study.

21 CFR 312.2(b)(1) criteria met - This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following apply: (i)The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; and (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

This is a clinical investigation of a drug product that is lawfully marketed in the United States and all the following apply:

- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation

is not intended to support a significant change in the advertising for the product;

- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

Will the drug/biologic be dispensed by the CUMC Research Pharmacy, which is responsible for the storage, handling, accountability, and dispensing of investigational drugs to research investigators? CUMC Research Pharmacy policy: https://researchpharmacy.cumc.columbia.edu/policies.html

No, the drug will not be dispensed by the Research Pharmacy

Please explain:

Fentanyl is not explicitly FDA-approved for intrathecal use but is extremely widely used for this purpose worldwide and at CUMC. There is an extensive body of literature supporting the use of fentanyl intrathecally in obstetric patients. Fentanyl is already routinely administered during spinal anesthesia for cervical cerclage at CUMC - it is not being used as an investigational drug, it is not being studied in this trial and does not need to be dispensed by the Research Pharmacy. Preparation by the Research Pharmacy and then transfer to investigators would be less safe than the manner in which the drug is already routinely prepared. The safest and most appropriate method of preparation will be the clinician drawing up the drug in a sterile fashion immediately before administration in the operating room, as is currently our routine practice. Adding a separate procedure with dispensing of the drug by the Research Pharmacy for a drug that is already routinely prepared and administered by clinicians could risk adding confusion to the process and decrease safety of administration.

Recruitment And Consent

Recruitment:

Will you obtain information or biospecimens for purposes of screening or determining eligibility?

No

Describe how participants will be recruited:

A member of the investigation team will approach patients to discuss the study and obtain written informed consent following the preoperative assessment and consent for anesthesia care for cervical cerclage.

Select all methods by which participants will be recruited:

[ ] Study does not involve recruitment procedures
[x] Person to Person
[ ] Radio
[ ] Newspapers
[ ] Direct Mail
[ ] Website
[ ] Email
[ ] Television
[ ] Telephone
[ ] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[ ] ResearchMatch
[ ] CUMC RecruitMe

Additional Study Information: Please add a description of your study as you would like it to be displayed on the RecruitMe website.

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[x] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:
The study in its entirety

Identify the portion of the study (e.g., prospective portion, focus groups, substudy 2) or subject population for which documentation of consent will be obtained::

Documentation of participation will be obtained from::
[x] Adult participants
[ ] Parent/Guardian providing permission for a child's involvement
[ ] Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:
A member of the investigation team who will be involved in the care of the patient will approach patients to discuss the study and obtain written informed consent following the preoperative assessment and consent for anesthesia care for cervical cerclage. A thorough explanation of the protocol will be given by the investigator. Same day consent is requested. Subjects must be recruited on the same day of care, since it is often not possible to know well in advance which patients will require cervical cerclage.

The consent process will include the IRB suggested language, including giving patients a clear opportunity to decline. Obstetric patients are frequently accompanied by family members and close friends, and their presence and participation will be encouraged during the informed consent discussion, unless of course the patient does not want such participation. Subjects will be given sufficient time to make a decision and will not be approached after administration of medications that may alter the cognitive state. We will document in the screening log, the time of start of the consent process and the time that consent was obtained.

[ ] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

[ ] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[ ] This is exempt research.

Subject Language
Enrollment of non-English speaking subjects is expected.

Languages anticipated:

Spanish

As you plan on enrolling non-English speaking subjects, administrative IRB approval of the translated documents (e.g., consent, recruitment materials, questionnaires) in the above selected languages are required. Please see the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details

(http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc).

Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

No

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

Our hypothesis is that the use of chloroprocaine for outpatient spinal anesthesia for cervical cerclage will lead to faster recovery of motor and sensory function than bupivacaine spinal anesthesia, which is currently the customary practice at CUMC. We believe CP spinal anesthesia, compared with the bupivacaine spinal anesthesia, will result in higher patient and higher staff satisfaction, and potentially economic benefits associated with earlier PACU discharge and decreased nursing staff workload. The primary outcome will be the mean difference between groups in time between the end of spinal injection (t IT) to time for no motor block (t motor), i.e. tIT - T motor. Secondary outcomes will include the time to ambulate and void (CUMC discharge criteria), rating of intraoperative discomfort, side effects and incidence of TNS.

Scientific Abstract:

Cervical insufficiency, defined as the inability of the uterine cervix to retain a pregnancy in the second trimester, in the absence of uterine contractions,[1] affects 1% of the obstetric population (about 1 in 500 pregnancies)[2] and 8% of populations with recurrent miscarriages and mid-trimester pregnancy losses.[3] Cervical cerclage is a surgical procedure performed via the vaginal route, whereby a suture is inserted at the junction of vagina and cervix, at the level of the internal os of the cervix, to provide mechanical support and prevent preterm birth. The procedure is usually performed as an elective outpatient procedure with a duration of approximately 30 minutes, but occasionally is performed as an emergency, in the case of threatened miscarriage. An anesthetic technique with a relatively short duration of action and recovery is indicated. Both regional and general anesthesia have been successfully used,[2] however spinal anesthesia is now overwhelmingly the choice, as it has the advantage of preserving maternal airway reflexes and limiting fetal exposure to anesthetic agents (although the procedure is usually performed beyond the stage of highest teratogenicity risk). Throughout most of the 1990s, lidocaine was the

intrathecal local anesthetic agent of choice for these procedures, but fell out of favor because of the frequency of reports of transient neurologic symptoms (TNS)- the reported incidence ranges from 10 – 40%.[4-6] Patients with TNS experience cramping, aching, or lancinating pain affecting the lower extremities and buttocks. Symptoms, which may have variable severity, occur within 6 - 36 hours after spinal anesthesia and last between 1 – 7 days. Bupivacaine is now the most common local anesthetic used for this procedure. Bupivacaine is associated with far less TNS but is a long-acting agent and carries the disadvantage of a prolonged anesthetic recovery, which is a source of significant patient dissatisfaction and impacts staffing and resources due to unnecessarily long post-anesthesia care unit (PACU) stays. In our practice at CUMC, with typical dosing of intrathecal hyperbaric bupivacaine 0.75% ranging from 7.5 – 9 mg, usually in conjunction with fentanyl 10 – 20 mcg, patients sometimes spend 5 hours or more in the PACU after a 30-minute outpatient cervical cerclage procedure. These prolonged stays are partly a consequence of the CUMC practice that maintains that patients must be able to void and ambulate independently prior to discharge home, due to concerns about the risk of falls and readmission for urinary retention. Chloroprocaine (2-chloroprocaine, CP) is an amino-ester local anesthetic with a fast onset and short duration that has made a resurgence for use in spinal anesthesia for ambulatory procedures.[7] Although safe reports of its use for spinal anesthesia were published following its introduction in 1952,[8] CP was never widely adopted, probably due to the availability of lidocaine, which had been introduced in 1949. The drug has had widespread use for epidural anesthesia, and due to its rapid onset and low systemic toxicity, is considered to be critical for the safe practice of obstetric anesthesiology (including at CUMC) for use in emergencies such as “stat” cesarean sections in women with epidural catheters in place for labor anlagesia. Serious concerns about the safety of the use of CP intrathecally arose in the wake of a series of case reports in the 1980’s of catastrophic neurologic sequelae, such as adhesive arachnoiditis, following the injection of large doses of the drug (average 611 mg) that had been meant to be injected into the epidural space.[9-11] Neurotoxicity was attributed to the preservative sodium bisulphite, which was hypothesized to provoke the release of sulphur dioxide, in the presence of the low pH of CP. Animal studies have been inconclusive, with conflicting results believed to be related to interspecies variation in levels of sulfur oxidase (catalyzes sulfites to sulfates), although variable results have also been seen in studies involving the same species.[12] The current formulation of CP has no additives. Vaghadia *et al.*[13] performed a recent trial involving 40 patients randomized to undergo transurethral resection of the prostate with spinal anesthesia with either preservative free CP or lidocaine. Several patients in the lidocaine group experienced TNS, and notably one patient in the CP group developed an incomplete cauda equina syndrome that developed 24 hours later and persisted for several weeks. The cause of that unfortunate complication is unclear. Contemporary reports of use spinal CP began to reappear in small studies in volunteers in the mid-2000’s and then larger studies followed, investigating its properties, such as minimum effective dose, and behavior with added dextrose and clonidine, as well as comparisons with bupivacaine and lidocaine.[14-26] This work supports the safety of the use of spinal CP, demonstrates the low incidence of TNS and particular suitability for surgeries in an ambulatory practice setting. CP is currently used very frequently at CUMC for spinal anesthesia for ambulatory surgical patients, especially for lower extremity orthopedic procedures such as knee arthroscopy. A Departmental review of CUMC practice between 2010 – 2013 reported 358 cases of in which CP has been used for spinal anesthesia, with no associated complications noted. [27] To our knowledge there are no published reports of the use of CP for spinal anesthesia for cervical cerclage or other outpatient procedures

in obstetric population. We plan to perform an observational study in which patients undergoing cervical cerclage under spinal anesthesia will be randomized to receive either plain 3% 2-chloroprocaine 50 mg or hyperbaric bupivacaine 9mg in conjunction with 15 mcg fentanyl. Our hypothesis is that the use of chloroprocaine for outpatient spinal anesthesia for cervical cerclage will lead to faster recovery of motor and sensory function than bupivacaine spinal anesthesia, which is currently the customary practice at CUMC. We believe CP spinal anesthesia, compared with the bupivacaine spinal anesthesia, will result in higher patient and higher staff satisfaction, and potentially economic benefits associated with earlier PACU discharge and decreased nursing staff workload.

Lay Abstract:

Cervical insufficiency, defined as the inability of the uterine cervix to retain a pregnancy in the second trimester, in the absence of uterine contractions, affects 1% of pregnant women. Cervical cerclage is a surgical procedure performed via the vaginal route, whereby a suture is inserted at the junction of vagina and cervix, to provide mechanical support and prevent preterm birth. The procedure is usually performed as an elective outpatient procedure with a duration of approximately 30 minutes, but occasionally is performed as an emergency, in the case of threatened miscarriage. Both regional and general anesthesia have been successfully used, however spinal anesthesia is now overwhelmingly the choice, as it allows the mother to breather on her own and limits the exposure of the fetus to anesthetic agents. Throughout most of the 1990s, lidocaine was the local anesthetic agent of choice for spinal anesthesia, but fell out of favor because of the frequency of reports of transient neurologic symptoms (TNS). Patients with TNS experience cramping, aching, or lancinating pain affecting the lower extremities and buttocks. Bupivacaine is now the most common local anesthetic used for this procedure. Bupivacaine is associated with far less TNS but is a long-acting agent and carries the disadvantage of a prolonged anesthetic recovery, which is a source of significant patient dissatisfaction and impacts staffing and resources due to unnecessarily long post-anesthesia care unit (PACU) stays. Chloroprocaine (2-chloroprocaine, CP) is an amino-ester local anesthetic with a fast onset and short duration that has made a resurgence for use in spinal anesthesia for ambulatory procedures. Serious concerns about the safety of the use of CP intrathecally arose in the wake of a series of case reports in the 1980's of catastrophic neurologic sequelae, such as adhesive arachnoiditis, following the injection of large doses of the drug (average 611 mg) that had been meant to be injected into the epidural space. Neurotoxicity was attributed to the preservative sodium bisulphite. The current formulation of CP has no additives. Contemporary reports of use spinal CP have been published since the mid-2000's and then larger studies followed, investigating its properties. This work supports the safety of the use of spinal CP, demonstrates the low incidence of TNS and particular suitability for surgeries in an ambulatory practice setting. CP is currently used very frequently at CUMC for spinal anesthesia for ambulatory surgical patients, especially for lower extremity orthopedic procedures such as knee arthroscopy. A Departmental review of CUMC practice between 2010 – 2013 reported 358 cases of in which CP has been used for spinal anesthesia, with no associated complications noted. To our knowledge there are no published reports of the use of CP for spinal anesthesia for cervical cerclage or other outpatient procedures in obstetric population. We plan to perform an observational study in which patients undergoing cervical cerclage under spinal anesthesia will be randomized to receive either plain 3% 2-chloroprocaine 50 mg or hyperbaric bupivacaine 9mg in conjunction with 15 mcg fentanyl. Our

hypothesis is that the use of chloroprocaine for outpatient spinal anesthesia for cervical cerclage will lead to faster recovery of motor and sensory function than bupivacaine spinal anesthesia, which is currently the customary practice at CUMC. We believe CP spinal anesthesia, compared with the bupivacaine spinal anesthesia, will result in higher patient and higher staff satisfaction, and potentially economic benefits associated with earlier PACU discharge and decreased nursing staff workload.

Risks, Benefits & Monitoring

Abbreviated Submission:
The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .
If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:
Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Spinal anesthesia is routinely performed for cervical cerclage at CUMC. Spinal anesthesia with either relatively low dose bupivacaine or choroprocaine is considered to be safe and does not present significant additional risk to receiving routine spinal anesthesia care at CUMC.

Potential Benefits:
Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Patients in the chloroprocaine group may benefit from earlier resolution of motor and sensory block and earlier discharge from the post-anesthesia care unit.

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Alternatives to not participating in the study are to receive spinal anesthesia with a local anesthetic agent chosen by the anesthesiology attending.

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

During the study period of approximately 24 hours, any data collection materials will be stored in a secure cupboard in a locked office on the CHONY Tower 10th floor, Room #1048. Following this period, once patient assessments have concluded, the cover sheet of the data collection instrument, indicating the patient name and ID number will be safely discarded and only de-identified data will be saved and discussed with investigators at this and other sites.No sensitive data or PHI will be stored or shared electronically. De-indentified data will be stored using the CUMC supported database system, RedCap, the data for which is stored on secure, encrypted servers.The principal investigator will be responsible for data and safety monitoring. The principal investigator, in conjunction with co-investigators will monitor closely for any issues, concerns or complications during follow-up of the patients. Patients will also be provided with the contact information of the principal investigator in order to report any unanticipated problems. Any unanticipated problems (i.e., events, outcomes, or occurrences that are unexpected, at least possibly related to the research, and suggest an increase in risk of harm to subjects or others) that arise will be reported to the IRB as soon as possible- by 1 week at the very latest.A data safety monitoring board has not been established for this project. Any adverse events will be immediately reported to the principal investigator. The principal investigator will also perform a biannual review of the data collected in order to identify unexpected issues.

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

50

Number enrolled to date:

43

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

20

Number anticipated to be enrolled in the next approval period:

7

Does this study involve screening/assessment procedures to determine subject eligibility?

Yes

Target accrual:

50

Number accrued to date:

43

Number accrued since the last renewal or, if this is the first renewal, since the initial approval:

20

Number anticipated to be accrued in the next approval period:

7

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

0

How many are off study?

44

How many completed the study?

43

Have any withdrawn of their own initiative?

No

Have any been removed by PI?

Yes

How many?

1

Please explain:

Unable to perform/complete study due to other issues to manage on the labor floor so patient had her cerclage anesthesia according to usual clinical care

Have any been lost to follow-up?

No

Have any died while on study?

No

Have any subject complaints been received?

No

Is this a multi-center study?

No

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase 1/2, sub-studies)?

No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:

Population Gender

Females	Males	Non Specific
100%	0%	0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	100%	0%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
0%	0%	0%	0%	0%	0%	100%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
0%	0%	100%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

Yes

What is the level of risk to the pregnant woman?

Minimal Risk

What is the level of risk to the fetus?

Minimal Risk

What is the level of risk to the neonate?

Minimal Risk

Indicate all groups for which there is a prospect of direct benefit:

[x]Pregnant women

[ ]Fetuses

[ ]Neonates

[ ]No prospect of direct benefit

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[ ]Individuals lacking capacity to provide consent

[ ]CU/NYPH Employees/Residents/Fellows/Interns/Students

[ ]Economically disadvantaged

[ ]Educationally disadvantaged

[x]Non-English speaking

Please ensure that your plan to enroll subjects in their primary language is described on the Informed Consent page.

[ ]Other Vulnerable populations

[ ]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

This study will be carried out in pregnant women undergoing cervical cerclage so necessitates a subject population that is exclusively pregnant women.

Does this study involve compensation or reimbursement to subjects?

No

Attached HIPAA Forms

Number	Type	Title	Status
AAAM9053	A	Chloroprocaine spinal anesthesia for cervical cerclage	Approve

Attached Consent Forms

Number	Copied From	Form Type	Title	Active/InActive	Initiator
AAAT6471	AAAT6471	Consent	Chloroprocaine spinal anesthesia for cerclage	Active	Richard Smiley (rms7)

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	Revised Consent Tracked Changes	Consent Form/Addendum	AAAQ0906_ICF_IRBTrackedChanges Lee 2_8_16.docx	Y		02/08/2016	Allison Lee (al3196)
No	AAAQ0906_ICF_IRBTrackedChanges	Consent Form/Addendum	AAAQ0906_ICF_IRBTrackedChanges.docx	N		01/28/2016	Diana Lesmes (dl3041)
No	Bupivacaine package insert	Investigator Brochure/Package Insert/Device Manual	Bupivacaine package insert Hospira.pdf	Y		10/07/2015	Allison Lee (al3196)
No	Chloroprocaine package insert	Investigator Brochure/Package Insert/Device Manual	Chloroprocaine package insert.pdf	Y		08/03/2015	Allison Lee (al3196)
No	Data Collection Sheet CP vs. Bupi PDF	Other	Data Collection Sheet CP vs. Bupi PDF.pdf	Y		01/27/2016	Yaritza Collazo (yr111)
No	Data collectio sheet 08/2017	Other	Data Collection Sheet CP vs. Bupi Revised_2017.pdf	Y	Y	08/18/2017	Richard Smiley (rms7)
No	Fentanyl Pkg Insert	Other	Fentanyl Pkg Insert.pdf	Y		01/27/2016	Yaritza Collazo (yr111)
No	Telephone Script	Other	Telephone Script.pdf	Y		01/27/2016	Yaritza Collazo (yr111)
No	Data Collection Sheet	Study Material/Instrument	Data Collection Sheet CP vs. Bupi PDF.pdf	Y	Y	10/07/2015	Allison Lee (al3196)