Title: Second-line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial
Sponsor Name: None
PI Name: Kim, Jimin **Protocol #:** 2018P000775 **Type:** Current View
Date Received: April 04, 2018

Study Staff

Name	Role	Degree	Organization	Citi Certified
Abel, Samantha	Co-Investigator		Mass General Brigham	04/27/21
Carusi, Daniela	Co-Investigator	MD, MSC	BWH > Obstetrics/Gynecology	01/25/22
Chyan, Arthur	Co-Investigator		Mass General Brigham	07/27/20
Combs, David	Co-Investigator		MGH > Anesthesia	04/10/20
Corey, Sarah	Research Assistant	Ph.D	BWH > Anesthesia	11/21/19
Farber, Michaela	Co-Investigator	MD, MS	BWH > Anesthesia	06/30/21
Fields, Kara	Statistician		Mass General Brigham	09/08/21
Gran, Monica	Co-Investigator		Mass General Brigham	08/24/21
Hale, John	Co-Investigator		Mass General Brigham	08/06/21
Justice, Samuel	Statistician		Mass General Brigham	09/03/21
Kim, Jimin	Principal Investigator		BWH > Anesthesia	08/13/19
Lumbreras-Marquez, Mario	Co-Investigator		BWH > Obstetrics/Gynecology > Other	09/22/20
Maeda, Ayumi	Co-Investigator		MGH > Anesthesia	07/18/20
Mendez-Pino, Laura	Research Assistant	MD	Mass General Brigham	04/19/22
Mohammadi, Somayeh	Co-Investigator		Mass General Brigham	06/17/21
Murthy, Anarghya	Research Assistant		Mass General Brigham	09/14/21
Seifert, Sara	Co-Investigator	MD	BWH > Anesthesia	05/26/20
Tsen, Lawrence	Co-Investigator	MD	BWH > Anesthesia	02/05/22
Villela Franyutti, Diego	Co-Investigator		Mass General Brigham	08/18/21
Yanik, Michelle	Co-Investigator		Mass General Brigham	08/24/21
Zhou, Jie	Co-Investigator	MD, MS	BWH > Anesthesia	08/23/19

Funding source

Record #	Fund	Project Period	PI Name	Sponsor	Record Type	Process	Link Date	Link Status
2019A009692	121504	07/01/19-06/30/21	Cole, Naida M	Brigham and Women's Hospital - Internal Funds	RM – Funded Agreement	AME22	12/26/19	Approved

Other Agreements

Record #	Fund	Project Period	PI Name	Sponsor	Record Type	Process	Link Date	Link Status
2022A006303			Kim, Jimin	Northwestern University	RM – DUA In	IR	04/27/22	Approved

Signatures

PI Name: Bateman, Brian T, MD
Authenticated: April 04, 2018
Department Chair: Body, Simon C, MD, MPH
Authenticated: April 04, 2018
PI Name: Cole, Naida M, MD
Authenticated: July 01, 2018
Department Chair: Tsen, Lawrence C, MD
Authenticated: July 02, 2018

InitialReview

Title:

Second-line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial

The Partners Human Research Committee has created several forms for review of human subjects research. This questionnaire includes a series of questions to identify the form (s) you need to complete for your research project.

1. Intervention/Interaction
2. Health / Medical Information
3. Excess Human Material and Related Health / Medical Information
4. Secondary Use of Research Samples and/or Data (samples/data from another research study)
5. Research Data Repository (collecting and storing health/medical information for future research)
6. Tissue or Sample Repository
7. Coordinating Center / Core Labs
8. Emergency / Single Patient Use of Investigational Products

1. Intervention and/or Interaction

Does your research involve an **intervention** and/or **interaction** with subjects for the collection of specimens or biological material or data (including health or clinical data, surveys, focus groups or observation or behavior)?

NOTE: Do not answer YES if this protocol is to establish a Research Data Repository or Sample/Tissue Repository. There are separate forms for Data and Tissue Repositories.

◉ Yes
○ No

Will the study population include **children**?

- ☐ Yes
- ◉ No

Will the study population include **adults with impaired decision-making capacity** for whom permission for participation will be obtained from their legally authorized representative (surrogate consent)?

- ☐ Yes
- ◉ No

Will the study population include **neonates of uncertain viability** and/or **nonviable neonates**?

- ☐ Yes
- ◉ No

Will the study population include **pregnant women** and/or **fetuses**?

- ◉ Yes
- ☐ No

Will the study population include any of the following:

- Patients who are in the hospital at any time during the study **(inpatients)**
- Patients seen in the **Emergency Department**
- **Patient Care Services Staff,** e.g. nursing staff asked to complete surveys on patient care or nursing practice

- ◉ Yes
- ☐ No

Will you be doing either of the following:

- **Testing a drug, biologic, dietary supplement or other agent** for safety and/or efficacy
- **Administering a drug, biologic, dietary supplement or other agent** to study human physiology

- ◉ Yes
- ☐ No

Will you be doing any of the following:

- **Testing a medical device** for safety and/or efficacy
- **Using a marketed device** in a non-standard (off-label) way
- **Using a commercially available device** that is not approved for use in humans

☐ Yes
◉ No

Will the study involve **ionizing radiation**, e.g. x-ray, radioactive drug, fluoroscopy?

☐ Yes
◉ No

Will the study involve **non-ionizing radiation**, e.g. MRI, ultrasound, laser, ultraviolet light emitting device or microwave?

☐ Yes
◉ No

Sponsor Funding: Brigham and Women's Hospital - Internal Funds [Internal]

Select the source of funding that will be used to support the proposed research:

☐ Government / Foundation / Other Non-Profit
☐ Corporate
◉ Institutional Award
☐ Department Funds
☐ None

Enter Peoplesoft fund # (if known):

Insight Agreement proposal number (read-only field):

2019A009692

Enter Principal Investigator name (if different):

Cole, Naida M

Medicare Coverage Analysis Requirement

Does the protocol for this study involve any items or services that will be billed to Medicare/private insurance, including study-specific procedures or those considered usual and customary care ("standard of care") outside the trial context?

☐ Yes
◉ No

NOTE: If you are unsure how to answer this question, please contact Sarah Bednar at Mass General Brigham Clinical Trials Office at 617-954-9364, or for NWH investigators, please contact Jayita Sen at 617-243-6517 for more information.

Is this the primary source of funding?

- ☐ Yes
- ☐ No
- ◉ Not applicable

Sponsor Funding: None

Select the source of funding that will be used to support the proposed research:

- ☐ Government / Foundation / Other Non-Profit
- ☐ Corporate
- ☐ Institutional Award
- ☐ Department Funds
- ◉ None

Is this the primary source of funding?

- ☐ Yes
- ☐ No
- ◉ Not applicable

Conflicts of Interest

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1. Is this study being funded or supported in whole or in part by an Outside Entity? **NOTE: Support includes providing funds, drug, device, or other resources. Outside Entity means any corporation, foundation or other entity or organization that is not a Mass General Brigham entity including any governmental entity or non-profit.**

- ☐ Yes
- ◉ No

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2. Are you studying or are you using in any significant way a drug or device or other technology that is owned, developed or licensed by an Outside Entity? **NOTE: Technology that is used in a significant way includes, for example, imaging equipment that, while not the focus of the study, is an important part of the study design and will need to be described and identified in the methods section of a publication. This includes licensed intellectual property such as patents, patent applications, and copyrighted materials, including technology licensed through Mass General Brigham.**

- ☐ Yes
- ◉ No

Study Details

Study Classification

The following information is being collected to allow the IRB to provide research administration with reports on the type of clinical research being conducted by Mass General Brigham investigators. This is self-reported information and will not affect what form questions you are presented with later in the application. Please select all that apply.

Type of Study: Select all that apply

Intervention

Therapeutic

Content of Study: Select all that apply

Pregnancy

Surgery

Will your research be **limited** to **any** of the following:

- Collection of one or more blood samples.
- Prospective collection of biological specimens for research purposes by noninvasive means.
- Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice.
- Collection of data from voice, video, digital, or image recordings made for research purposes.
- Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

☐ Yes
◉ No

NOTE: You must attach a detailed protocol on the attachments page of this submission using the Attachment Type 'Detailed Protocol.'

Is this a **randomized controlled clinical trial**?

☐ Yes
◉ No

Does the research involve the use of **human embryonic stem cells?**

☐ Yes
◉ No

Does the research involve issues related to **women's health**?

◉ Yes
☐ No

Is this a **cancer-related** trial?

- ☐ Yes
- ◉ No

NOTE: Cancer-related means the primary focus is cancer therapy OR the targeted population is only cancer patients (patients with diagnosed malignancy). Most oncology / cancer-related research studies are reviewed by the DFCI IRB. See the MGB IRB Oncology / Cancer Research Guidance BEFORE continuing with this IRB submission.

Study Design

Who designed the study?

- ☐ Cooperative Group / Consortium
- ☐ Corporate Sponsor
- ◉ Mass General Brigham Investigator
- ☐ Other

NOTE: When the corporate sponsor designs the study, the corporate sponsor's protocol must be submitted to the IRB for review. Before the research can begin, the IRB must approve the sponsor's protocol and Mass General Brigham Clinical Research Office must execute the Agreement with the sponsor.

Will any data generated from this study be submitted to the FDA?

- ☐ Yes
- ◉ No

Clinical Trials Registration

Clinical Trials Registration and Results Reporting

Investigator–initiated clinical trials must be registered on ClinicalTrials.gov to comply with federal FDA requirements in FDA 42 CFR 11 (Final Rule) and/or NIH Policy. Studies that falls under both FDA and NIH requirements only need to be registered once. The information posted on ClinicalTrials.gov (CT.gov) must be updated and verified at least every 12 months.

The following information is used to identify studies that require clinical trials registration and results reporting, and to inform Principal Investigators (PI) of their responsibilities for registration and results reporting.

IMPORTANT NOTE: Even if your investigator-initiated clinical trial does not meet the NIH or FDA clinical trials registration requirements, you are strongly advised to read and consider registering your trial to comply with the following additional requirements:

- **A non-federal sponsor may require registration as part of the award's terms and conditions**
- **International Committee of Medical Journal Editors (ICMJE) for publication purposes**
- **Center for Medicare & Medicaid for research billing claims for qualifying clinical trials (Mass General Brigham Clinical Trials Office will notify you if applicable)**
- **Research funders now requiring registration and results reporting: May 18, 2017 Joint Statement**

For additional information, please see the Human Research Affairs Compliance and Education Office website for Clinical Trials Registration.

Is this a Mass General Brigham investigator – initiated research study?

- ○ No
- ◉ Yes

Is this research funded in whole or in part by NIH **AND** does this research meet the NIH's definition of **clinical trial**?

NIH defines a clinical trial as any research study that meets all of the following criteria:

- The study involves human participants;
- The participants are prospectively assigned to an intervention;
- The study is designed to evaluate the effect of the intervention on participants; **AND**
- The effect being evaluated is a health-related, biomedical or behavioral outcome.

- ◉ No
- ○ Yes

Is the study an **interventional clinical trial**?

In the FDA Final Rule with respect to a clinical study or clinical investigation,

- **Interventional** is defined to mean that participants are assigned prospectively to an intervention or interventions according to a protocol to evaluate the effect of the intervention(s) on biomedical or other health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65140-41]
- **Clinical Trial** is defined as a clinical investigation or a clinical study in which human subject(s) are prospectively assigned, according to a protocol, to one or more interventions (or no interventions) to evaluate the effect(s) of the intervention(s) on biomedical or health-related outcomes. [Source: 42 CFR 11.10(a); 81 FR 65139]

- ○ No
- ◉ Yes

Does this research evaluate at least one **drug, biological** or **device product** regulated by the United States Food and Drug Administration (U.S. FDA)?

- **FDA regulated** includes both approved and investigational drugs, biologics and device.
- A **device product** regulated by FDA, includes significant risk devices for which approval of an IDE is required by FDA, non-significant risk devices that are considered

to have an approved IDE in accordance with 21 CFR 812.2(b), or device products that are exempt from the submission requirements of 21 CFR part 812. [Source: 81 FR 65012]

- A **drug product** regulated by the FDA includes a drug that is the subject of an approved NDA [new drug application] or BLA [biologic license application] or that would require an approved NDA or BLA to be legally marketed in the United States. A non-prescription drug product that is or could be marketed under an existing over-the-counter drug monograph is **not** considered an Applicable Clinical Trial (ACT). [Source: 81 FR 65041]

○ No
◉ Yes

Is the study other than a **phase** 1 trial of a drug and/or biological product or is the study other than a device feasibility study?

- **Study phase** means, for a clinical trial of a drug product (including a biological product), the numerical phase of such clinical trial, consistent with terminology in 21 CFR 312.21, such as phase 2 or phase 3, and in 21 CFR 312.85 for phase 4 studies. [Source: 42 CFR 11.10(b)(6); 71 FR 65141]

- **Device feasibility** means a device is being evaluated for the feasibility of the product or of a test prototype device and not health outcomes. [Source: 81 FR 65035]

◉ Yes
○ No

Do **ANY** of the following apply? Answer **YES** if the answer to at least **ONE** of the following three questions is **YES**.

- Is at least one study facility located in the United States or a U.S. territory?
- Is the study conducted under a U.S. FDA Investigational New Drug application or Investigational Device Exemption?
- Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?

○ No
◉ Yes

The responses to the questions above indicate this study meets the FDA Final Rule requirements for clinical trials registration. Mass General Brigham Institutions have delegated responsibility for clinical trials registration, periodic updates, and results and adverse event reporting to the Principal Investigator ('Responsible Party'). This study must be registered on ClinicalTrials.gov prior to the first subject being enrolled into the study.

Responsible Party

Enter Name of MGB investigator who will be the Responsible Party, for example, Jane Doe, MD:

Jimin Kim, MD

Enter the full name of the MGB Institution of the MGB investigator, for example, Massachusetts General Hospital:

Brigham and Women's Hospital

Documentation of ClinicalTrials.gov Registration

Have you submitted registration information to ClinicalTrials.gov?

○ No
◉ Yes

Indicate if a National Clinical Trial (NCT) registration number has been assigned:

◉ Assigned
○ Pending

Enter the NCT number; for example NCT12345678:

NCT03584854

Results Reporting

ClinicalTrials.gov results reporting is required within 12 months of the primary endpoint completion date defined as the date that the final subject was examined or received the intervention for the purposes of collection of primary outcome. Early consultation is strongly advised. Please contact the QI Program for assistance:

Mass General Brigham Human Research Quality Improvement (QI) Program: humanresearchqi@partners.org

Additional information can be found at:
QI Program website
www.ClinicalTrials.gov

Study Population

How many subjects do you plan to enroll at Mass General Brigham' sites?

950

NOTE: Target enrollment at Mass General Brigham sites is the number of subjects you expect to provide written or verbal consent, or implied consent by voluntary completion of a survey or participation in a focus group.

How many subjects will be enrolled study-wide?

1250

What is the age range of eligible subjects who will be enrolled at Mass General Brigham sites?

Enter 'None' if there is no maximum age.

Minimum age:

18

Maximum age:

50

Equitable Selection of Subjects

Will both males and females be enrolled?

- ○ Yes
- ◉ No

Which gender will be enrolled?

- ◉ Females only
- ○ Males only

Indicate below whether the study population that is being targeted for the research is any of the following groups that require additional protections:

- ☐ Children (less than 18 years of age)
- ☐ Economically or Educationally Disadvantaged
- ☐ Embryos
- ☐ Employees under the direct supervision of the investigators conducting the research
- ☐ Employees (physician, nurses, or other healthcare workers) in the course of, or related to, their employment related duties
- ☐ Individuals with Impaired Decision-Making Capacity
- ☐ Neonates -age up to 28 days
- ☐ Non-English Speakers
- ☐ Patients from the Medical Practice of the Investigator
- ☑ Pregnant Women / Fetuses
- ☐ Prisoners
- ☐ Students of Harvard Medical School
- ☐ U.S. Military Personnel
- ☐ None of the above

Performance Sites / Facilities

Where will investigators covered by this IRB consent/enroll subjects and perform study procedures?

☑ BWH

BWH facilities/resources. Check all that apply.

- ☐ Emergency Department
- ☐ Clinical Trials Center
- ☐ Health Centers
- ☐ Inpatient
- ☑ Labor & Delivery / Post Partum Floors
- ☐ NICU
- ☑ Operating Room / Recovery Room
- ☐ Outpatient

☐ Faulkner
☐ MEE
☐ MGH
☐ NSMC
☐ NWH
☐ PCHI
☐ Shriners
☐ SRH
☐ IHP
☐ McLean
☐ Broad Institute
☐ Network Sites (e.g. NeuroNEXT and Stride)
☐ Off-site Research (off-site means sites other than those owned or controlled by Mass General Brigham entities)

NOTE: When more than one Mass General Brigham site is included in the submission, designate a Site-Responsible Investigator (not Residents, Fellows, or Trainees) for each site on the Staff & Access page.

Is this a Mass General Brigham investigator-initiated multi-site study?

◉ Yes
○ No

Enter the name of each of the institutions/entities where informed consent will be obtained and where study procedures will be performed by investigators who are **not** affiliated with Mass General Brigham System.

Northwestern Memorial Hospital

Enter the Institution Federal Wide Assurance number (FWA), if applicable:

FWA00001550

NOTE: A list of OHRP-approved assurances (FWA) is available on the OHRP website.

Enter the IRB Contact for the Institution:

Heather Yates, IRB coordinator; heather.yates@northwestern.edu

Enter the IRB contact phone number:

678-983-8964

NOTE: Investigators who are not affiliated with Mass General Brigham System must obtain IRB approval from their own institution. These investigators should not be listed on the Staff & Access page. Each non-affiliated performance site must submit documentation of local IRB approval to the Mass General Brigham PI prior to initiation of the research at that site. Attach or forward copies of IRB approval to the MGB IRB when received from the performance site(s).

Recruitment

Source of Subjects

Indicate whether you will use any of the following resources to identify prospective subjects:

- ☐ Census / Public Records
- ☐ Commercial Mailing Lists
- ☐ Emergency Department
- ☐ Inpatient Units
- ☑ Medical Records
- ☑ Outpatient Clinics
- ☑ Primary Physician / Physician Specialist
- ☐ Registries / Patient Databases (e.g. cancer registry)
- ☐ Research Patient Data Registry (RPDR)
- ☐ Research Match (Vanderbilt Recruitment Tool)
- ☐ RSVP for Health
- ☐ Research Studies
- ☐ None of the above

Note: For more information about ResearchMatch, see https://www.researchmatch.org/about/

Methods / Materials

Indicate whether you will use any of the following methods / materials to recruit subjects:

- ☐ Advertisements - E-Mail
- ☐ Advertisements - Internet
- ☐ Advertisements - Rally https://rally.partners.org (Contact rallyforresearch@partners.org for more information)
- ☐ Advertisements - Newspaper (e.g. Metro, Boston Globe)
- ☐ Advertisements - Radio
- ☐ Advertisements - Television
- ☑ Flyers / Postings (e.g. within BWH or MGH)
- ☐ Patient Gateway - Personalized Letters
- ☐ Patient Gateway - Targeted Research Announcements
- ☐ Mail
- ☐ ResearchMatch Volunteer Message (see https://www.researchmatch.org/researchers/)
- ☐ Telephone Calls to Prospective Subjects (who have previously agreed to be contacted, e.g. RSVP for Health)
- ☐ None of the above

NOTES:

1. **The text of all advertisements, letters, and telephone calls/scripts used to recruit subjects must be submitted for IRB approval. You may attach these documents to the application on the Attachments page. For guidance on recruitment and advertising, please see the following MGB IRB web pages Recruitment of Research Subjects and Guidelines for Advertisements for Recruiting Subjects.**
2. **When using Research Match, you must submit the contact message template for Research Match advertisement to the IRB for approval. The contact message template is available to registered researchers on the ResearchMatch website.**

Pre-Screen of Subjects During Recruitment

Will you ask prospective subjects pre-screening questions over the phone to determine eligibility?

- ☐ Yes
- ◉ No

Will you ask prospective subjects to complete an online pre-screening tool to determine eligibility?

- ◉ Yes
- ☐ No

Note: Refer to Mass General Brigham Guidance on Pre-Screening of Subjects During Recruitment.

Remuneration

Will subjects be paid or receive any type of remuneration / compensation for their time and expenses?

- ☐ Yes
- ◉ No

Informed Consent

For guidance, refer to the MGB IRB web page Informed Consent of Research Subjects.

Will informed consent and authorization for participation in research be obtained **verbally (oral consent)**, or by use of a **written consent form** approved by the MGB IRB and signed by the subject or the subject's legally authorized representative?

- ◉ Yes
- ☐ No

Indicate how informed consent and authorization will be obtained:

- ◉ Written
- ☐ Verbal (oral consent)

Enter the description of the study population (as listed on page 1 of the informed consent) for each consent form.

Indicate who will obtain the informed consent of the subject or the subject's legally authorized representative.

- ☑ Licensed Physician Investigator
- ☐ Non-Physician Investigator
- ☐ Other

Indicate from whom informed consent will be obtained. Check all that apply:

- ☑ Adult Subject
- ☐ Parent(s) / Guardian for Child
- ☐ Court-Appointed Guardian for Adult
- ☐ Surrogate for Adult, other than Guardian (e.g. health care proxy, person with durable power of attorney, spouse, adult child, or close family member).

NOTE: When surrogate consent for adults is obtained, the individuals with impaired decision-making capacity form must be completed. For guidance, refer to the following MGB IRB web pages, Surrogate Consent to Research for Individuals with Impaired Decision-making Capacity

Will the research target a non-English speaking group?

- ○ Yes
- ◉ No

NOTE: When investigators can reasonably expect that more than an incidental number of subjects speaking the same non-English language will be enrolled (for example, if the research is targeting a non-English speaking group), the use of a written translation of the entire English version of the consent form is required. The MGB IRB must approve all written translated versions of the consent from and recommends that the written translation be done by an in-house medical translator from Interpreter Services or other qualified person or service recommended by Interpreter Services. Refer to the MGB IRB guidance on Obtaining And Documenting Informed Consent Of Subjects Who Do Not Speak English.

Will a study subject advocate participate in the consent process?

- ○ Yes
- ◉ No

NOTE: A study subject advocate may be used, for example, because subjects have limited time to consider participation in a study involving significant risk, or may feel obligated to participate.

Will subjects have less than 12 hours to decide whether or not to participate?

- ○ Yes
- ◉ No

NOTE: The IRB may waive the requirement to obtain a signed written consent / authorization form if it finds either: (1) the only record linking the subject and the research is the consent form and the principal risk would be potential harm resulting from a breach in confidentiality; or (2) the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

Diaries

Will subjects be asked to complete a diary(ies)? For example, a drug diary, pain diary, symptom diary, etc.

- ☐ Yes
- ◉ No

Privacy / Confidentiality

Health/Medical Records

Will medical history / clinical information be obtained from the subject's health / medical record for study purposes?

- ◉ Yes
- ☐ No

Explain what information will be abstracted from health / medical records:

Basic patient demographic information, pertinent medical history, details of their pregnancy, labor and delivery, peripartum laboratory values and postpartum outcomes will be abstracted and recorded.

Will sensitive personal health information resulting from this study become part of the subject's health/medical record?

- ☐ Yes
- ◉ No

Sensitive personal information obtained for research purposes typically does not become part of the subject's health/medical record. Rather, these data are retained in the research records only.

NOTE: Certain categories of medical information are commonly recognized as potentially sensitive, such as information related to mental health; sexual behaviors or sexual orientation; illegal behaviors; and substance abuse. Some genetic test results may be viewed similarly. When applicable, investigators are reminded to inform subjects in the consent form that sensitive personal health information may become part of their health/medical record, e.g., routine testing for HIV infection.

Will you enroll subjects in the study in Epic?

- ☐ Yes
- ◉ No

NOTE: Epic is both the Mass General Brigham electronic medical record and the billing system, including research billing. For more information about Epic/eCare, refer to Research Information Services & Computing's Support & Training page eCare Research FAQs.

Do you consider this to be a sensitive study that requires the title of the study be masked in the electronic medical record (eCare)?

- ☐ Yes
- ◉ No

NOTE: The title of studies determined to be sensitive will be masked in the Mass General Brigham eCare system (e.g., Psychiatry Study 1 will appear as MGB 2017P001234). The IRB is responsible for making the final determination whether a study is sensitive. Examples of studies that may be considered sensitive are studies that collect information about:

- **sexual practice**
- **sexual victimization**
- **illegal behaviors**
- **alcohol, drugs, or other addictive products**
- **stigmatizing illnesses**

Certificate of Confidentiality

NIH funded research that collects or uses **identifiable sensitive information** is automatically issued a Certificate of Confidentiality as part of the terms and conditions of the award. The NIH considers research that is reviewed by the IRB to involve identifiable sensitive information requiring a Certificate.

If you do **NOT** have NIH funding, do you have or do you plan to obtain a Certificate of Confidentiality to protect the data from disclosure (e.g., by court order or subpoena)?

- ☐ Yes
- ◉ No

NOTE: For information on Certificates of Confidentiality, refer to the OHRP website.

Sending Health Information to Research Collaborators Outside Mass General Brigham

Will identifiable information be shared with research collaborators **outside** Mass General Brigham?

- ☐ Yes
- ◉ No

NOTE: Data that includes any of the identifiers listed below are considered identifiable.

- **Names, including initials**
- **Social security numbers**
- **Medical record numbers**
- **Addresses by street location**

- **Addresses by city, county, precinct, zip code**
- **All elements of dates (except year) related directly to individuals including, but not limited to, dates of birth, death, admission, discharge, or any service**
- **All ages over 89 and all elements of dates (including year) indicative of such age**
- **Telephone numbers**
- **FAX numbers**
- **Electronic email addresses**
- **Web URLs**
- **Internet protocol (IP) addresses**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identification numbers and serial numbers including license plates**
- **Medical device identifiers and serial numbers**
- **Biometric identifiers, including finger and voice prints**
- **Full face photographs and any other comparable images**
- **Any other unique identifying numbers, characteristics or codes including, but not limited to, globally unique identifiers (GUID) and universally unique identifiers (UUID) or equivalent**

For guidance, refer to the MGB IRB web page on the HIPAA Privacy Rule.

NOTE: Non-institutional email services are not approved to transmit confidential data. Use "Send Secure" to transmit confidential data to non-institutional email domains (e.g., gmail, yahoo, icloud, etc.). For more information on appropriate methods of transmitting research information/data to research collaborators, refer to the Research Information & Computing website.

Business Associates

Will identifiable information be shared with persons or entities outside of Mass General Brigham who are not research collaborators or who are not part of the research team, but who will perform some aspect of the research on behalf of Mass General Brigham, e.g., a private recruitment agency, outside laboratory or data analysis group?

- ☐ Yes
- ◉ No

NOTE: In this situation, the persons or entities referred to above are considered business associates of Mass General Brigham, therefore a Business Associate Agreement is required.

Instruments / Questionnaires

Will the research involve the development of instruments, questionnaires, surveys, interviews, and/or focus group topics?

- ☐ Yes
- ◉ No

Will the research involve the use of instruments, questionnaires, surveys, interviews, and/or focus group topics?

- ☐ Yes
- ◉ No

Ancillary Drugs

Will you be using FDA-approved drugs for research-related ancillary/supportive care?

- ☐ Yes
- ◉ No

NOTE: An ancillary drug is a commercially available drug that is being used for a research-related ancillary test or for supportive care (e.g. methacholine challenge tests, lidocaine for research-related biopsies, EMLA cream for venipuncture, contrast agent for scans or x-rays). The Research Consent Form should include the risks of ancillary drugs being administered as part of the research.

Ancillary Devices

Will any non-hospital inventory FDA-approved medical devices be used to obtain measurements, collect data, or monitor subjects?

- ☐ Yes
- ◉ No

NOTE: When the sponsor (or another party) provides a medical device for use to obtain measurements, collect data, or monitor subjects, the investigator must request a zero dollar purchase order to track receipt of the medical device and to document BME inspection for electrical safety, when necessary. For more information, refer to the Zero Dollar Purchase Order Policy.

Non-Intervention / Non-Interaction Group

In addition to the intervention/interaction group that provides informed consent to participate in the research, do you plan to also review the health/medical records or other private/confidential information of any subjects **with whom you will have no contact at any time**?

- ☐ Yes
- ◉ No

Pregnant Women or Human Fetuses

Federal regulations require the IRB to provide additional protections for pregnant women and human fetuses involved in research [45 CFR 46.204].

Assessing Risks And Benefits
When assessing risks and benefits, consider the variability in health status of the subjects to be enrolled, their medical experiences, and the extent to which the research procedures will be a burden to the subjects in the context of their daily lives and/or routine medical care. Procedures that usually present no more than minimal risk include: urinalysis, obtaining a small amount of blood, EEGs, allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. The assessment of the probability and magnitude of the risk, however, may vary depending on the diseases or conditions the subjects may have.

Minimal Risk
As defined in the regulations 45 CFR 46.102(i), “minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Pregnant women or fetuses may be involved in research if **all** of the following conditions listed below are met [45 CFR 46.204]. **Please provide study-specific information with your explanations.**

(a) Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies (including studies on non-pregnant women) have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

Provide a brief description of relevant prior pre-clinical and clinical studies, and based on this information, what you think the risks to pregnant women and to the fetus are in your research.

This study will prospectively evaluate the clinical efficacy of methylergonovine compared to carboprost. The two agents are used as second-line uterotonics in the case of atonic postpartum hemorrhage (PPH) refractory to oxytocin, but it is unclear which is the more effective drug for this indication. One recent observational study suggests that methylergonovine may be superior to carboprost in reducing PPH-related morbidity, although residual confounding may be responsible for this finding. [Butwick et al. Am J Obstet Gynecol 2015] There are no randomized trials comparing clinical outcomes of methylergonovine vs carboprost in PPH to date.

The most recent American College of Obstetricians and Gynecologists Practice Bulletin makes no recommendation on which second-line uterotonic agents to administer preferentially in the absence of contraindications. Given this, we believe there will be no added risk to pregnant women experiencing atonic PPH by receiving methylergonovine or carboprost in a randomized manner.

(b) The risk to the fetus is caused solely by the interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; if there is no such prospect of direct benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means.

Does the research hold out the prospect of direct benefit for the woman, or to the fetus?

- ◉ Yes
- ○ No

Explain what direct benefit may accrue to the women taking part in this research, or to the fetuses.

Treatment with second-line uterotonics (methylergonovine or carboprost) has the potential to save a mother's life in cases of severe postpartum hemorrhage (PPH). Both of these drugs will be available to all study participants, but the order in which they are eligible to receive either drug will be randomized. They will receive one or both medications in a timely manner to stop bleeding. Any additional interventions will be offered as per usual standard of care at our hospital.

(c) Any risk is the least possible for achieving the objectives of the research.

Explain how the risks have been minimized to the least possible to achieve the research objectives.

Patients will be given information about the study prior to their admission, as well as at the time of consent for participation. They will have the opportunity to ask questions and clarify the details regarding participation in the study. Patients will be given a written consent form to sign, which will list

all possible risks of study participation. A physician investigator will be present at all times during the consent process, enrollment and conduct of the study.

Patients will receive standard care in all aspects except the order in which they receive two clinically equivalent 2nd-line uterotonics. If at any time a patient wishes to withdraw from the study, they may do so voluntarily. The principal investigator will review study records after every 5 new patients enrolled. The principal investigator will take full responsibility for standardized review of recruitment at the above frequency, to ensure adherence to protocol, detection of minor or major adverse events (AEs), and timely reporting of such events to the IRB with halting of the study if necessary (for any AEs).

Informed Consent

Check all that apply:

- ☑ Informed consent will be obtained from the **pregnant woman** in accordance with the consent provisions of Federal regulation 45 CFR 46.116.
- □ When the research holds out the prospect of **direct benefit solely to the fetus**, informed consent will be obtained from the **father** in accordance with the consent provisions of 45 CFR 46.116, except, if he is unable to consent because of unavailability, incompetence, or temporary incapacity, or the pregnancy resulted from rape or incest.
- ☑ **Each individual providing consent will be fully informed** regarding the reasonably foreseeable impact of the research on the fetus. This information is included in the Mass General Brigham Research Consent Form.

MASSACHUSETTS GENERAL LAW CHAPTER 112, SECTION 12J

Experimentation on human fetuses prohibited; medical procedures authorized; consent; approval; civil and criminal liability and proceedings; severability.

(a)I. No person shall use any live human fetus whether before or after expulsion from its mother's womb for scientific, laboratory, research or other kind of experimentation. This section shall not prohibit procedures incident to the study of a human fetus while it is in its mother's womb, provided that in the best medical judgment of the physician, made at the time of the study, said procedures do not substantially jeopardize the life or health of the fetus, and provided said fetus is not the subject of a planned abortion.
(a)II. No experimentation may knowingly be performed upon a dead fetus unless the consent of the mother has first been obtained, provided, however, that such consent shall not be required in the case of a routine pathological study.
(a)III. No person shall perform or offer to perform an abortion where part or all of the consideration for said performance is that the fetal remains may be used for experimentation or other kind of research or study.

Nursing Implementation and Planning

Emergency Department / Inpatient Research

Will subjects be recruited from the Emergency Department or be inpatients while on study?

- ○ Yes
- ◉ No

Patient Care / Nursing Practice Research

Will nursing staff be asked to complete surveys on patient care or nursing practices?

- ○ Yes

◉ No

Drugs / Biologics / Dietary Supplements: Carboprost Tromethamine

NOTE: Do not complete this form for FDA-approved drugs administered for ancillary tests / supportive care, e.g. methacholine challenge tests, lidocaine for research-related biopsies, contrast agents.

Manufacturer Information

Name:

PHARMACIA UPJOHN, CO

Type of Agent

Select:

◉ Drug
○ Biologic
○ Dietary Supplement
○ Stable Isotope

FDA Status of Drug

Select:

◉ Marketed Drug (FDA-approved for sale by prescription or over-the-counter)
○ Not Marketed Drug (Not FDA-approved for sale by prescription or over-the-counter)

Indication for Use of Drug

Select:

◉ The drug will be used for an indication in the approved labeling
○ The drug will be used for a non-approved indication (off-label)

Explain the indication for use of drug in this study:

Carboprost is used for the treatment of postpartum hemorrhage due to atony that is refractory to oxytocin.

Is the drug a Schedule II narcotic?

○ Yes
◉ No

NOTE: For a list of Schedule drugs, refer to the US Department of Justice web page.

Investigational New Drug

Will this agent be studied under an IND?

- ○ Yes
- ◉ No

Study Phase / Design

Select the study phase (if applicable):

- ○ Phase 1
- ○ Phase I / II
- ○ Phase II
- ○ Phase II / III
- ○ Phase III
- ○ Phase III / IV
- ◉ Phase IV
- ○ Pilot
- ○ Treatment IND

Indicate the study design:

- ☑ Randomized
- ☐ Single Blind
- ☑ Double Blind
- ☐ Open Label
- ☐ Placebo-Controlled
- ☐ Multi-Center
- ☐ Cross Over
- ☐ Dose-Finding

Agent Formulation

Do you know how the drug is packaged and what form it is in?

- ◉ Yes
- ○ No

Enter the number of units, for example for 50 mg, type '50'

250

Select the form of the agent:

Ampoule

Select the agent units:

mcg

Agent Dispensing

Indicate where the agent will be housed and dispensed:

- ☐ Faulkner Pharmacy

- ☐ MGH Research Pharmacy
- ☐ McLean Pharmacy
- ☐ NSMC Pharmacy
- ☐ NWH Pharmacy
- ☐ SRH Pharmacy
- ☐ MEE Pharmacy
- ☑ Other

Specify where the agent will be housed and dispensed:

The agents are kept as standard 'emergency' medications in the omnicell directly outside the operating rooms on the L&D floor at BWH. Each study drug (as determined by randomization) will be accessed directly from this omnicell by the anesthesiologist (or a non-study member of the anesthesia team taking care of the patient) at the time of obstetrician's request for a second-line uterotonic. It will be labelled, dispensed and documented in the chart in usual fashion (unblinded) by the anesthesiologist. The anesthesiologist will not reveal the identity of the drug to the rest of the O.R. team.

- ☐ BWH Investigational Drug Service

Agent Preparation

Will the Research Pharmacy be responsible for preparation of the dose?

- ○ Yes
- ◉ No

Agent Storage Requirements (following shipment)

Check all that apply:

- ☐ Room Temperature
- ☐ Stored in locked vault or cabinet
- ☑ Refrigerator (36 - 46F or 2-8C)
- ☐ -20C Freezer
- ☐ -40 C Freezer (available at BWH only)
- ☐ -80C Freezer
- ☐ Other

NOTE: For studies involving the use of drugs and/or biologics, the following must be submitted for the IRB review: investigational drug brochure or equivalent information, product information (package insert or equivalent on marketed products). These documents may be attached in the "Attachments" section of this application.

Drugs / Biologics / Dietary Supplements: Methylergonovine

NOTE: Do not complete this form for FDA-approved drugs administered for ancillary tests / supportive care, e.g. methacholine challenge tests, lidocaine for research-related biopsies, contrast agents.

Manufacturer Information

Name:

NOVARTIS

Type of Agent

Select:

- (•) Drug
- ( ) Biologic
- ( ) Dietary Supplement
- ( ) Stable Isotope

FDA Status of Drug

Select:

- (•) Marketed Drug (FDA-approved for sale by prescription or over-the-counter)
- ( ) Not Marketed Drug (Not FDA-approved for sale by prescription or over-the-counter)

Indication for Use of Drug

Select:

- (•) The drug will be used for an indication in the approved labeling
- ( ) The drug will be used for a non-approved indication (off-label)

Explain the indication for use of drug in this study:

Methylergonovine is used for the treatment of postpartum hemorrhage due to atony that is refractory to oxytocin.

Is the drug a Schedule II narcotic?

- ( ) Yes
- (•) No

NOTE: For a list of Schedule drugs, refer to the US Department of Justice web page.

Investigational New Drug

Will this agent be studied under an IND?

- ( ) Yes
- (•) No

Study Phase / Design

Select the study phase (if applicable):

- ( ) Phase 1
- ( ) Phase I / II
- ( ) Phase II

- ○ Phase II / III
- ○ Phase III
- ○ Phase III / IV
- ◉ Phase IV
- ○ Pilot
- ○ Treatment IND

Indicate the study design:

- ☑ Randomized
- ☐ Single Blind
- ☑ Double Blind
- ☐ Open Label
- ☐ Placebo-Controlled
- ☐ Multi-Center
- ☐ Cross Over
- ☐ Dose-Finding

Agent Formulation

Do you know how the drug is packaged and what form it is in?

- ◉ Yes
- ○ No

Enter the number of units, for example for 50 mg, type '50'

0.2

Select the form of the agent:

Vial

Select the agent units:

mg

Agent Dispensing

Indicate where the agent will be housed and dispensed:

- ☐ Faulkner Pharmacy
- ☐ MGH Research Pharmacy
- ☐ McLean Pharmacy
- ☐ NSMC Pharmacy
- ☐ NWH Pharmacy
- ☐ SRH Pharmacy
- ☐ MEE Pharmacy
- ☑ Other

Specify where the agent will be housed and dispensed:

The agents are kept as standard 'emergency' medications in the omnicell directly outside the operating rooms on the L&D floor at BWH. Each study drug (as determined by randomization) will

be accessed directly from this omnicell by the anesthesiologist (or a non-study member of the anesthesia team taking care of the patient) at the time of obstetrician's request for a second-line uterotonic. It will be labelled, dispensed and documented in the chart in usual fashion (unblinded) by the anesthesiologist. The anesthesiologist will not reveal the identity of the drug to the rest of the O.R. team.

- ☐ BWH Investigational Drug Service

Agent Preparation

Will the Research Pharmacy be responsible for preparation of the dose?

- ○ Yes
- ◉ No

Agent Storage Requirements (following shipment)

Check all that apply:

- ☐ Room Temperature
- ☐ Stored in locked vault or cabinet
- ☑ Refrigerator (36 - 46F or 2-8C)
- ☐ -20C Freezer
- ☐ -40 C Freezer (available at BWH only)
- ☐ -80C Freezer
- ☐ Other

NOTE: For studies involving the use of drugs and/or biologics, the following must be submitted for the IRB review: investigational drug brochure or equivalent information, product information (package insert or equivalent on marketed products). These documents may be attached in the "Attachments" section of this application.

Attachments

Name	Mode
8.17.2021 Consent Form - CLEAN	Electronic
04.19.22 Methergine Hemabate IRB Detailed Protocol--CLEAN (Detailed Protocol)	Electronic
Second-Line Uterotonics- Data Collection Sheet (Data Collection Form)	Electronic
Uterine Tone Score Intraop Data Collection_4.29.19 (Data Collection Form)	Electronic
8.17.2021 Flier- CLEAN (Flyer)	Electronic
8.17.2021 18-24 Hour Interview Guide- CLEAN (Instrument/Questionnaire)	Electronic
8.17.2021 2-4 Hour Interview Guide - CLEAN (Instrument/Questionnaire)	Electronic
Continuing Review Adverse Event Attestation (Other)	Electronic
Correspondence_for_STU00214439 (Other)	Electronic
Methergine Package Insert (Package Insert)	Electronic

Name	Mode
Hemabate Package Insert (Package Insert)	Electronic
04.19.22 Protocol Summary-CLEAN (Protocol Summary)	Electronic
8.17.2021 Email to Patients- Uterotonics Study CLEAN (Recruitment Letter)	Electronic

Protocol Title: Second-Line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial

Principal Investigator: Jimin Kim, MD

Site Principal Investigator: Jimin Kim, MD

Description of Subject Population: Pregnant women undergoing non-emergent cesarean section delivery at BWH

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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

Why is this research study being done?

The purpose of this study is to compare how well 2 FDA-approved drugs, methylergonovine and carboprost, work to stop excessive bleeding after delivery. Most of the time when women have too much bleeding after delivery, it is because the uterus does not contract effectively. Currently, if there is too much bleeding after delivery, we use either one of these drugs to stop the bleeding,

but it is not known which drug is better. The decision to use one drug or the other is based on physician's preferences and institutional customs, since there are no national or international guidelines recommending the use of one over the other.

We are asking you to take part in this study because you are going to have a cesarean section delivery. Patients who have this surgery may have too much bleeding right afterwards, and we would like to find out what is the best drug to treat this bleeding, if it happens.

About 100 patients will take part in this study.

How long will I take part in this research study?

You will be involved in the study during the time of your cesarean section from the time your baby is born until the end of the surgery.

What will happen in this research study?

If you appear to be eligible and are interested in participating, we will explain the study to you once you are in hospital and preparing for your cesarean section. If you choose to take part in this study, we will ask you to sign this consent form.

When you have your baby in the operating room, you will receive a drug called oxytocin as part of the standard of care. This drug is given during every cesarean section immediately after your baby is delivered, in order to help the uterus contract well, to prevent bleeding from poor uterus contraction. Oxytocin is also the first line treatment for poor uterine contraction. It is possible that even with oxytocin being given, the surgeon may think your bleeding is higher than normal. If so, they will take several steps to control the bleeding. One of these steps may be giving you a drug to stop the bleeding. If the doctors want one of these drugs, we will assign you by chance (like flipping a coin) to receive either methylergonovine or carboprost.

If any more drugs are needed to stop the bleeding after that first drug, you will receive the other study drug, as would typically be done. Your obstetrician and the nurses in the operating room will not know which drug you receive until after the surgery is completed. The anesthesiologist will know which drug they are giving to you and will document it in your surgical record. Patients in both groups will receive every usual measure of care during their cesarean section and after surgery. Being in the study will not change the medications you receive or anything about

your surgical treatment. The only difference for study patients is that the order in which they get the drugs to stop bleeding will be 'by chance'.

At the time of giving the first drug for bleeding, the anesthesiologist will ask the obstetrician to rate the 'uterine tone', which is a measure of how much your uterus has contracted. The more the contraction, the less bleeding you should have. At 10 minutes later, the anesthesiologist will again ask the obstetrician to rate the uterine tone, to see if it has improved because of the drug they gave.

If you receive the study drug(s), we will collect your basic medical history and the results of your blood testing. We will also document information about how your surgery and recovery go. All this information will be recorded in a secure electronic document on a password-protected computer. The only people with access to this information will be two study investigators.

At any time, if you wish you may stop being in the study. Your decision will not affect your future care in any way. You will continue to receive medications and other treatments to prevent and stop bleeding, whether or not you choose to take part in the study.

Also, your participation in this study may be stopped by the study doctor or the institutional review board for any of the following reasons:
• If the study procedures appear to be medically harmful to you
• If it is discovered that you do not meet the study requirements
• If it is determined to be in your best interest
• We stop doing the study for other reasons

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example: list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

What are the risks and possible discomforts from being in this research study?

The two drugs used in this study are methylergonovine and carboprost. Serious side effects are rare, but may occur in some instances.

Methylergonovine
The most common side effect of methylergonovine is high blood pressure, which in severe cases, may be associated with seizures. Other side effects may include:
- headache
- abdominal pain
- nausea, vomiting or diarrhea

Rare side effects include:
- heart attack or chest pain
- rapid or slow heart rate
- shortness of breath
- blood in the urine
- hallucination
- allergic reaction
- leg cramps
- ringing in the ears

Stroke, numbness and tingling, and dangerous heart rhythms have been reported in patients who received methylergonovine.
The onset of methylergonovine is approximately 2-5 minutes and the effects of methylergonovine should last no more than 3-6 hours.

Carboprost
The most common side effects of carboprost are flushing, nausea, vomiting and diarrhea and fever. Additional side effects may include:
- asthma, difficulty breathing or cough
- high blood pressure, palpitations, chest pain or fast heart rate
- anxiety, dizziness, drowsiness, shivering
- rash
- hot flash, increased thirst
- stomach pain, urinary or uterine infection
- back pain, leg cramps, muscle pain
- blurry vision or eye pain

Rare reports have occurred of severe allergic reaction to carboprost.

If you have any of these symptoms or any other side effects after receiving one or both of the study drugs, you should tell your study doctor right away. You should tell your doctors about all

medications that you are taking (both prescribed and over the counter) to ensure that these drugs are safe for you to receive.

There is a small risk of loss of confidentiality. We will minimize this risk by keeping all records with your identifying information in a secure and locked area.

What are the possible benefits from being in this research study?

The information gained from this study may benefit future patients by improving our current treatment of bleeding after delivery, allowing us to be more effective in stopping this bleeding. However, you may not directly benefit from participating in this study.

What other treatments or procedures are available for my condition?

You do not have to participate in this study to be treated for bleeding after delivery. You will receive all standard treatments that are needed to control any bleeding that occurs.
When there is abnormal bleeding after delivery, several measures are taken to control bleeding, such as medications to stop the bleeding and sometimes additional surgery. In addition to the 2 study drugs, methylergonovine and carboprost, other medications used to treat bleeding are:
Oxytocin
Misoprostol

Additional surgical options may include:

- Placement of a balloon in the uterus
- Exploratory laparotomy, an operation done on the abdomen in order for the surgeon to determine the cause of bleeding and fix it
- Uterine artery embolization, a minimally invasive procedure done under X-ray, with a needle placed in the groin and small particles sent through it to the blood supply of the uterus to stop the bleeding in the place it occurs
- B-Lynch sutures, a technique for sewing temporary stitches into the uterus to compress it and stop severe bleeding
- Dilation and evacuation, a surgery in which the obstetrician dilates the cervix and then uses instruments to enter the uterus and remove any products of conception that remain inside which are causing bleeding
- Hysterectomy, a surgery to remove the uterus in cases of uncontrollable bleeding

Oxytocin is the first and best treatment to prevent and control bleeding after delivery; you will receive this drug first, as is standard after all deliveries. If you need additional medication to control bleeding, you will receive one of the study drugs, methylergonovine and/or carboprost, as part of your participation in this research. If you need additional treatment afterward, misoprostol and repeat doses of the prior drugs will be available to you. Additional surgery may be performed if needed.
Talk with the study doctor if you have questions about any of these treatments or procedures.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

No payment will be given for participating in this study.

What will I have to pay for if I take part in this research study?

There are no costs to you for participating in this research study. You will not pay for any study-related items and services. We may bill your health insurer for, among other things, routine items

and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for routine care or other billed care, in the same way that you would be responsible for these payments if you did not take part in the research. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Dr. **Jimin Kim**, MD is the person in charge of this research study. You can call her at **773-960-4237** M-F 8-5 or after hours have her paged by calling 617-732-6660. You can also call Dr Brian Bateman or Dr Julian Robinson M-F between 8am-5pm at 617-732-5500 with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call Dr **Jimin Kim**, MD at **773-960-4237** .

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.

- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other: none

Some people or groups who get your health information might not have to follow the same privacy rules that we follow and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in

charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

_____	_____	_____
Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

Consent Form Version: 8/17/2021

DETAILED PROTOCOL
Second-line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial

Version date: 04/19/2022

I. BACKGROUND AND SIGNIFICANCE

Primary postpartum hemorrhage (PPH) is defined by the American College of Obstetricians and Gynecologists as a cumulative blood loss of >1000mL within 24 hours of the birth process. PPH remains the leading source of maternal morbidity and mortality worldwide with uterine atony identified as the underlying cause in up to 80% of cases.[1] [2]Between 1994 and 2006, the rate of PPH increased by 42% in the United States, raising further concern for this problem.[3]

Treatment of PPH typically begins with administration of exogenous oxytocin, a hormone responsible for uterine contraction. Oxytocin is given prophylactically during the third stage of labor to decrease the risk of PPH and is considered the first-line medical treatment for PPH.[4] When postpartum bleeding persists despite oxytocin administration, a multidisciplinary approach combining mechanical, pharmacologic, and surgical measures is indicated. Approximately 3-25% of PPH cases require a second-line uterotonic agent in addition to oxytocin, with the two most commonly administered second-line agents in the U.S.A. being methylergonovine maleate (methylergonovine) and 15-methyl prostaglandin F2α (carboprost).[5] The comparative efficacy of these two drugs is unknown and as a result, there is wide variability in the usage of these second-line uterotonics.[6]

The most recent American College of Obstetricians and Gynecologists Practice Bulletin makes no recommendation on which second-line uterotonic agents to administer preferentially in the absence of contraindications.[7] Given the equivalent role for these two agents, the decision to use either methylergonovine or carboprost is usually based on provider preference in the absence of any contraindications. Internationally, there is a similar lack of consensus, with guidelines recommending oxytocin, methylergonovine, carboprost, or misoprostol in varying order.

Recent evidence suggests that methylergonovine is the most commonly used second-line uterotonic agent across the United States with carboprost being the next most frequent.[5,8] One recent observational study suggests that methylergonovine may be superior to carboprost in reducing PPH-related morbidity, although residual confounding may be responsible for this finding.[9] There are no randomized trials comparing clinical outcomes of methylergonovine vs carboprost in PPH to date. Since PPH remains an unpredictable and emergent event, high quality prospective trials are challenging to perform and scarce. This research is nonetheless critical to provide high quality evidence for the optimal management of atonic PPH.

The aim of this study is to evaluate in a randomized fashion the comparative efficacy of methylergonovine and carboprost for treating atonic PPH. In the event of PPH, patients undergoing non-emergent cesarean section (C/S) with no contraindications to either drug will be randomized to receive one of the two equivalent agents in a blinded fashion after oxytocin. All patients will be managed as per standard of care at the Brigham and Women's Hospital. The uterine tone will be estimated by a blinded obstetrician before and after study drug administration. Several secondary outcomes relevant to efficacy and safety of the drugs will also be evaluated.

II. **SPECIFIC AIMS** (Research Objectives)

We hypothesize that the administration of methergonovine will be associated with a 1 point greater reduction in uterine tone (on a 0-10 scale) at 10 minutes after administration compared to carboprost.

1. The primary outcome will be the uterine tone score on a 0 to 10 scale 10 minutes after administering the study drug. A score of 0 will mean the uterus has 'no tone'. A score of 10 will mean there is 'excellent tone'.

2. Secondary outcomes will include:
    a) change in uterine tone from the time of study drug administration to 5 minutes later,
    b) administration of an additional uterotonic agent after the first study drug
    c) number of transfused blood products within 24 hours from the time of delivery,
    d) any surgical intervention intended to control bleeding: i.e. Bakri balloon, O'Leary stitch, d&e, exploratory laparotomy, B-Lynch sutures, hysterectomy or interventional radiology artery embolization,
    e) intraoperative quantitatively measured blood loss (QBL),
    f) pre-delivery to postpartum change in serum hemoglobin,
    g) vasopressor requirement or hypovolemic shock
    h) postpartum admission to the intensive care unit (ICU),
    i) need for postoperative mechanical ventilation,
    j) nausea, vomiting, or diarrhea, abdominal pain, shortness of breath, headache, blurred vision, anxiety, chest pain, sweating, or palpitations within 2 hours postpartum
    k) hypertensive emergency (SBP>/=160 or DBP>/=110)
    l) EKG changes indicative of myocardial ischemia,
    m) acute renal dysfunction,
    n) length of postoperative hospital stay,
    o) postpartum acute lung injury or circulatory fluid overload in the context of blood product transfusion,
    p) allergic reaction deemed the result of blood product transfusion

III. SUBJECT SELECTION

Inclusion Criteria/Exclusion Criteria:
Inclusion criteria will be all of the following: American Society of Anesthesiologists (ASA) I, II or III health status (minimal to no systemic disease), age between 18 and 50 yrs, and planned elective C/S or non-emergent C/S after labor, with suspected uterine atony at the time of delivery despite the administration of oxytocin.

Exclusion criteria for enrollment in the study will include any of the following: patients with essential hypertension or any hypertensive disorder of pregnancy, patients with cardiovascular disease, patients with active asthma (i.e. bronchodilator usage in the past 24 months), non-English speaking patients who are undergoing urgent, non-scheduled C/S, patients who refuse to accept blood transfusion (e.g. Jehovah's Witnesses), patients with a known coagulopathy or abnormal baseline coagulation profile, patients with known or suspected hypersensitivity to either of the two study drugs, and patients with known or suspected delayed PPH after leaving the operating room from the cesarean delivery.

Source of Subjects and Recruitment Methods:
Subjects will be recruited from women admitted to the labor & delivery (L&D) floor at the Brigham and Women's Hospital undergoing cesarean delivery who meet selection criteria as above.

IV. SUBJECT ENROLLMENT

Prior to admission, all participating obstetricians will provide their patients with the study Flier and consent form, which will be given to patients at their 28-week obstetric visit. This will allow potential subjects ample time to consider participation in the study. In addition, participating obstetricians will request consent from their patients to be contacted for research purposes, to provide a reminder of the study protocol closer to patients' delivery date. Those patients who agree to be contacted and are at 37 weeks gestational age or greater and eligible for the study (planning either vaginal or cesarean delivery) will be sent an email with the study's Flier and consent form attached from the research assistant. The email will be sent securely to protect patient confidentiality, in accordance with MGB Privacy and Security guidelines.

At the time of admission to the pre-operative area or labor and delivery unit, patients will be pre-screened for eligibility using the OB Pre-Screen questionnaire. The screening process will be documented in a Pre Screening Log without patient identifiers (patients will be logged using the first initial of their last name). All eligible patients undergoing planned elective C/S will be provided the Flier and consent form. A physician investigator (either the principal investigator or one of the co-investigators) who is not involved in the patient's care will review and discuss the study plan at this time, allowing subjects the opportunity to ask questions and address any of their concerns or any issues surrounding the study. Non-English speaking patients undergoing planned elective C/S will be interviewed with the assistance of an official in-person BWH medical interpreter. The consent will be verbally translated in full to their native language by the interpreter. Subjects interested in participating will then be consented by the principal investigator or physician co-investigator and enrolled in the study.

In the setting of the current COVID-19 pandemic, all study staff will wear appropriate PPE (as dictated by Partners-wide official policy) while working and during any conversation with study subjects. In addition, patients will only be approached in their room by a study physician to minimize personal contact, at which time they will discuss the study and obtain informed consent from those patients interested in participation. There will be attention to appropriate social distancing, hand hygiene and minimization of sharing any physical objects (e.g. pen, clipboard etc.) throughout the conversation with prospective study subjects. Should patients be interested in participation, written consent will be accepted.

Patients who are designated to have a C/S delivery after labor due to 'failure to progress' will be approached in a similar manner for consent at the time of decision for C/S. Non-English speaking patients undergoing unscheduled, urgent C/S will not be approached since translators may not be available in a timely fashion to assist with consent.

This study will only be conducted in women. Non-English speaking patients undergoing urgent C/S will not be approached since translators may not be available in a timely fashion to assist with consent. No other vulnerable populations will be specifically targeted, nor will any one group bear a disproportionate share of the burdens or benefits of the research.

A total of 1250 women will be enrolled, and 100 randomized in this study based on the power calculation included below and allowing for patient withdrawal or loss to followup; women will be assessed for eligibility and then randomized to either methylergovonive or carboprost groups with the aim of approximately 50 patients per group.

V. STUDY PROCEDURES

All subjects will have an IV placed and baseline labs sent, as is standard for all patients admitted to the Center for Women and Newborns Labor and Delivery unit. Baseline labs will include: type and screen and complete blood count (CBC).

At the time of delivery, enrolled subjects will be assessed for poor uterine tone despite the administration of oxytocin following delivery. If either methylergonovine or carboprost is requested by the obstetrician or anesthesiologist, subjects will then be randomized by the anesthesiologist to either "methylergovonine" or "carboprost" groups by a computer generated randomization scheme printed on a piece of paper in a sealed envelope. The anesthesiologist will then withdraw the appointed medication (based on subject randomization) from the O.R. omnicell and administer it without revealing to anyone in the O.R. which drug was given. They will document the medication in the subject's Epic record in the usual fashion.

The obstetrician and nurse, involved in the cases as well as the study investigator will be blinded to the study group assignments. All physician co-investigators (with the exception of the principal investigator) and the statistician will be blinded to study group assignments throughout the study. As such, these co-investigators will not be involved in the obstetric care of the study subjects, with the following one exception: Every effort will be made to keep the study investigator who consented the subject out of the operating room and uninvolved in the subject's clinical care in all cases. However occasionally, due to staffing challenges and clinical acuity of a patient's case (e.g. massive hemorrhage), the anesthesiology attending or fellow who consented the patient may need to be involved in the patient's intraoperative or postoperative care. To minimize any chance of patient coercion and bias in clinical decision-making, the consent process will occur first with the study investigator anesthesia provider. Only after consent is complete and the patient enrolled will the same anesthesiologist who consented the patient end up caring for the patient. This scenario will only occur in situations when a staffing shortage occurs or the case requires additional help due to a life-threatening situation. Everything possible will be done to avoid that situation. Thus the patient will agree to participate in the study in advance of forming any physician-patient relationship with the study investigator, and the study investigator will only affect clinical care as a helper in case of clinical necessity, not as the leader of clinical decision-making (i.e. the study investigator will not be the primary anesthesiologist of record for the case).

The study drug will consist of either:

1. 0.2mg methylergovonine, or
2. 0.25mg 15-methyl prostaglandin F2α

The anesthesiologist will administer the study medication in a 1mL syringe intramuscularly in the patient's deltoid muscle. Each patient will have both medications available in the fridge where hemorrhage medications are stored, so that the second of the 2 drugs can be easily administered in succession if an additional agent is needed.

At the time of administration of the first study drug, the anesthesiologist will ask the obstetrician to rate the uterine tone on a scale of 0 to 10 (0 being with 'no tone', 10 being 'excellent tone'). The anesthesiologist will then set a timer. After administration of the study drug, patient care will receive our usual standard of care. At 5 and 10 minutes from the onset of timing, the anesthesiologist will once again ask the obstetrician for a rating of uterine tone between 0 and 10. These values will be recorded by the anesthesiologist on a Uterine Tone Score Intraop Data Collection sheet included in the sealed envelope provided by the investigator.

If an additional uterotonic agent is requested by the obstetrician, the unblinded anesthesiologist will prepare the other drug, again in a-1mL syringe. Timing of this administration will be noted on the study record sheet. All other medications and interventions will proceed as usual and in an unblinded fashion.; If uterine tone remains unsatisfactory, identity of the study drugs will remain blinded, if possible. Any repeat administrations of carboprost or methylergonovine will be given by the anesthesiologist based on the timing of administration of the 2nd study drug.

The obstetric physicians and nurses caring for the patient will document quantitatively measured blood loss during the delivery. The volume of blood mixed with amniotic fluid in the graduated suction jars and the number of sponges soaked with blood will be noted. In addition to baseline serum hematocrit, postpartum serum hematocrit and platelet count, will be evaluated on the first postoperative day after C/S. The change in serum hematocrit will be compared among study groups.

At the end of the C/S, the anesthesiologist will complete the Randomization Sheet, documenting the patient MRN and study ID number. They will return the Randomization sheet and the Uterine Tone Score Intraop Data Collection sheet in the [previously sealed] envelope to a locked room on L&D where all paper documents for the study will be temporarily stored until the unblinded principal investigator collects the sheets (on the same day as subject enrollment) and brings them to a locked filing cabinet in a locked office to which only the principal investigator has access.

Within the first 24 hours after delivery, but no sooner than the time of patient transfer from the labor and delivery floor to the postpartum unit, Between 2-4 hours postpartum and again between 18-24 hours postpartum, a blinded study investigator who is not involved in the subject's clinical care will interview the patient by phone (to avoid physical contact and minimize the risk for COVID-10 transmission) and record the information from the interview on the corresponding '2-4 Hr Interview Guide' or '18-24 Hr Interview Guide'. This will allow them to assess subjective side effects of the study medication such as G.I. upset, dizziness, shortness of breath, palpitations or chest pain. Non-English speaking patients will be interviewed in person with the assistance of an in-person interpreter from BWH Interpreter Services.

Subject randomization, patient MRN and the linked study ID number will be documented on a separate form in the secure electronic database, REDCap database by the unblinded principal investigator. This form will be visible only to the principal investigator. An unblinded study investigator (i.e. the principal investigator, or a research assistant, when one is hired in the future) with access to REDCap will be responsible for collecting and entering all primary and secondary outcomes from the Uterine Tone Score Intraop Data Collection sheet, the 2-4 Hour Interview Guide and the 18-24 Hour Interview Guide and Epic medical records (including side-effects of study medications) into REDCap. Subject randomization will be documented, on a separate form in the database to which only the principal investigator has access, in order to preserve the integrity of the data collection and entry.

The need for blood product administration and quantity of each component given within 24hrs after cesarean section will be recorded. In addition, the investigator will record any additional interventions performed to halt bleeding, such as Bakri balloon placement, B-Lynch sutures, uterine artery embolization or hysterectomy.

Total intravenous fluids given from start to conclusion of the delivery will be recorded. The use of vasopressors, uterotonic agents, anti-emetic agents will be recorded. Length of stay and any postoperative complications occurring during the hospital stay will be documented at the time of hospital discharge.

All clinical and other data obtained during this study will be considered confidential. Procedures to limit access to subject charts and information from the study will be in place. Study participant data will be de-

identified upon entry into the data collection tool and will be known only to the investigators. No information regarding the identity of individual subjects will be utilized for publications.

Primary Endpoint

1. Uterine tone score as recorded at 10 minutes following the administration of the second-line uterotonic.

Secondary Endpoints

1. Need for an additional uterotonic agent after the study drug,
2. Uterine tone score as recorded at 5 minutes following the administration of the second-line uterotonic,
3. Number of units of blood products transfused from t_0 to t_{final} (t_0 = time of delivery; t_{final} = 24 hours after delivery)
4. Need for a surgical or radiologic intervention to control bleeding.
5. Quantitative intrapartum blood loss
6. Pre- vs post-delivery hemoglobin values.
7. Maternal morbidity: admission to the intensive care unit postpartum, postoperative infection, transfusion reaction, acute kidney injury, hypovolemic shock, or vasopressor requirement, study medication side effects.

Subject Costs

There will be no extra costs to the subjects related to the conduct of this study, as there are no additional medications or tests to be used that are not already the routine standard of care. Methylergonovine and carboprost used in the study will be stocked as needed by the inpatient hospital pharmacy in the usual manner. Subjects and/or their insurance companies will be responsible for all their medical and surgical procedures and care as associated with their delivery.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g., data collection sheets).

Baseline patient characteristics will be collected and documented on data collection sheets. These characteristics will include:

1. patient MRN
2. randomization group
3. age
4. height, weight, BMI
5. gravidity and parity
6. baseline hematocrit and platelet count measured at the time of admission or on the day of delivery

b. Statistical methods

The balance of patient characteristics between the two groups before intervention will be evaluated using standardized differences. Shapiro-Wilk test will be used to confirm whether the primary endpoint, uterine tone score 10 minutes after drug administration, satisfies the normality assumption. Multiple linear regression will be conducted when normality assumption satisfied. In the case when the normality assumption is not established, log transformation/box-cox transformation of the outcome will be carried out before modeling. For secondary endpoints that are dichotomous, logistic regression will be used to

examine the intervention effect after adjusting for potential confounders. For continuous secondary endpoints, such as intrapartum blood loss, we will evaluate its distribution before performing appropriate modeling. Trial site will be included as a covariate in all models to adjust for the stratification of randomization by hospital.

c. Power analysis (e.g., sample size, evaluable subjects, etc.)

Assuming a common within-group standard deviation in uterine tone score of 1.9 points, a minimum sample size of 41 randomized patients per group would provide 80% power at a two-sided alpha level of 0.05 to detect a 1.2 point difference in mean uterine tone score at 10 minutes post secondary uterotonic administration between groups using a two-sample t-test. A total of 50 patients per group (100 patients total) will need to be randomized be enrolled to account for protocol violations. Since we currently perform 175 C/S monthly at BWH, and approximately 20 patients undergoing non-emergent C/S receive methergine or hemabate for uterine atony each month, we anticipate needing to enroll 1250 patients in total to be able to randomize 100 patients to receive the study intervention.

The within-group standard deviation estimate of 1.9 is based on the observed standard deviation in uterine tone score (averaged between raters) at 10 minutes post-delivery amongst patients in our previous study (The Inter-rater Reliability of a 0 to 10 Uterine Tone Score) who received a secondary uterotonic. The minimal clinically important difference of 1.2 points is based on the upper limit of the 90% confidence interval for the difference in uterine tone score (averaged between raters) at 3 minutes post-delivery between patients who did and did not receive a secondary uterotonic (difference in means [90% CI]: -2.3 [-3.5, -1.2]).

VII. RISKS AND DISCOMFORTS

Adverse reactions to methylergonovine include increased blood pressure, seizure, dizziness and headache, and nausea, vomiting, diarrhea and abdominal pain from uterine contractions. Rare effects include chest pain, myocardial infarction, coronary vasospasm, tachycardia, dyspnea, and hematuria. A large retrospective study of over 2 million parturients found no significantly increased risk of acute coronary syndrome or acute myocardial infarction after receiving methylergonovine.[10] ACOG recommendations nonetheless state that methylergonovine should be avoided in patients with hypertension and cardiovascular disease.[7]

The most common adverse reactions to carboprost include nausea, vomiting, diarrhea, as well as headache, myalgias, increased temperature and flushing. Due to its stimulation of smooth muscle contraction, modest increases in blood pressure may be seen, but these are generally clinically insignificant. Additionally, bronchospasm, abnormal ventilation-perfusion and hypoxia may occur, and may be particularly severe in patients susceptible to these complications. Carboprost is therefore contraindicated in patients with active asthma.

Patients with any contraindication to either of the study drugs will be excluded from participation in the study. Patients with a diagnosis of asthma will be interviewed to confirm if their asthma is active. Any patient who has used a bronchodilator within the past 24 months will be considered to have active asthma and will be excluded. If a patient carries a diagnosis of ‘childhood asthma’ and/or has not needed a bronchodilator for >24 months, they will be considered eligible to participate in the study. After enrollment, patients will be evaluated for all of the above side effects by a clinical investigator between at time of transfer to the postpartum floor and again between 18 to 24 hours after delivery. The obstetric 6-

week postpartum follow-up record will be reviewed by a clinical investigator to screen for thrombotic events or other side effects.

Administration of methylergonovine and carboprost will occur after delivery of the fetus. Single intramuscular doses of methylergonovine have been shown to decrease serum prolactin levels compared to women receiving placebo. However, milk production, rates of exclusive breastfeeding and infant weigh gain have not been found to differ.[11-15] Case reports indicate a possible association of methylergonovine with tachycardia, vomiting, diarrhea and agitation in the infant. A recent prospective observational study comparing postpartum use of methylergonovine with control found no difference in lactation or neonatal complications in the infants of mothers who received methylergonovine.[16]

It is unknown whether carboprost is excreted in human milk and there are currently no studies determining the infant risk from carboprost in breastfeeding mothers.

No additional inpatient hospital time is anticipated by participating in this study.

VIII. POTENTIAL BENEFITS

The potential benefits of receiving methylergonovine or carboprost during cesarean delivery include a reduction in PPH, a lower risk of transfusion requirement and other interventions used to control PPH.

On a population-based level, the potential benefit of this study lies in an improvement in our understanding and management of PPH by determining the superior second-line uterotonic between methylergonovine and carboprost. This in turn could lead to a significant decrease in maternal morbidity due to adverse events associated with PPH.

IX. MONITORING AND QUALITY ASSURANCE

A physician investigator will be present during the entire consent, enrollment and conduct of the study. Criteria for early termination from the study will be observed. Two definitions of early endpoints will be utilized:

1. Subject decision for withdrawal from participation at any time.
2. Any operative or medical condition changes prior to or during the entire study period deemed unacceptable by the obstetrician, anesthesiologist, or physician investigator.

The principal investigator will review all forms and data with every 5th subject to ensure completeness, accuracy and adherence to the protocol. There will be no data safety monitoring board (DSMB) in this study. In place of a DSMB, the Principal Investigator will take full responsibility for standardized review of recruitment at the above frequency, to ensure adherence to protocol, detection of minor or major adverse events (AE's), and timely reporting of such events to the IRB with halting of the study if necessary (for any AE's).

All AE's, whether or not they are considered related to the study, shall be recorded on the Adverse Experience Form within the Case Report Forms (CRFs). The study investigators will comply with the Food and Drug Administration (FDA) regulations requiring the expedited reporting of any AE that is Serious, Unexpected, and Associated with the use of the study drug. AEs will be reported to the PHRC in accordance with the PHRC Policy on Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events.

Serious AE's include hemodynamic instability requiring epinephrine or norepinephrine or resulting in loss of consciousness or cardiovascular collapse, allergic or anaphylactic reactions to study solution infused, major respiratory complication during hospital admission, or seizure activity. Should any of these events occur, the Principal Investigator will be contacted immediately, the study code broken, and the case reviewed. Serious AE's that occur higher than the expected native incidence will warrant temporarily halting the study and consultation with the Directors of Obstetric Anesthesia (Brian Bateman, MD) and Labor and Delivery (Julian Robinson, MD).

The standard causality criteria will be used to determine these AE's. Investigators will notify the principal investigator immediately of all SAEs. If necessary, any additional relevant information will be collected and reported. All AE's will be reported to the IRB per the HRC guidelines.

X. REFERENCES

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MRN	Study Number	DOB	DOS	Surgeons	Anesthesiologist

		INTRAOP				
Study Number	Preop Hct	5 Min Tone	10 Min Tone	2nd Study Drug Given?	Misoprostol	QBL

Crystalloid	Colloid	RBCs	FFP	Platelets	TXA	Riastap	UOP	Pressors (total mg)	Ischemic EKG Changes

INTRA/POST	6hrs POSTOP	24hrs POSTOP				
Surgical or IR Interventions	Hct	QBL	RBCs	FFP	Platelets	TXA

Riastap	Pressors	Misoprostol

Study Number	Nausea	Vomiting	Diarrhea	Dyspnea	Headache	Blurred Vision

Severe Anxiety	Chest Pain	Diaphoresis	SBP>/=160	If>160, Max SBP	DBP>/=110,

If>110, Max DBP	Avg UOP/hr

Study Number	Hospital LOS	ICU Admission	Hypovolemic Shock (blood loss + signs end organ malperfusion)	Postop Mechanical Ventilation	TRALI/TACO

Allergic Transfusion Reaction	Other Transfusion-related or Bleeding Complications

Study Number:

Time	0 min	5 min	10 min
Score			

2nd Uterotonic? (Y / N)
Timing of 2nd drug (if given):
Ischemic changes (ECG changes)? (Y / N)
QBL (including amniotic fluid):
Estimated Amniotic Fluid volume:

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- You will receive all the usual treatments for bleeding, but the or which you receive the 2 interchangeable medications will be pr decided
- Your medical information will be examined by additional doctor assured, this information is ALWAYS kept confidential

Please help us keep moms safe after delivery! To learn mor

To find out if this study is right for you, please contact

Jimin Kim, MD, Email: jjkim@bwh.harvard.edu, Location: CWN L1, 75 Francis Street, Boston MA 02115

18-24 HR POSTPARTUM
BLINDED INTERVIEW GUIDE
SECOND-LINE UTEROTONICS in PPH STUDY

Please DO NOT access the patient's record prior to completing this form!

Did the patient have any of the following before transfer to the postpartum floor?

	YES	NO
Nausea?	☐	☐
Vomiting?	☐	☐
Diarrhea?	☐	☐
Shortness of Breath?	☐	☐
Headache?	☐	☐
Blurred Vision?	☐	☐
Severe Anxiety?	☐	☐
Chest Pain?	☐	☐
Abnormal Sweating?	☐	☐

Patient Name: _____

MRN: _____

Study Number: _____

Date/Time of Interview: _____

Questions or Concerns:
Jimin Kim, MD
e: jjkim@bwh.harvard.edu
pg: 38918

2-4 HR POSTPARTUM
BLINDED INTERVIEW GUIDE
SECOND-LINE UTEROTONICS in PPH STUDY

Please DO NOT access the patient's record prior to completing this form!

Did the patient have any of the following before transfer to the postpartum floor?

	YES	NO
Nausea?	☐	☐
Vomiting?	☐	☐
Diarrhea?	☐	☐
Shortness of Breath?	☐	☐
Headache?	☐	☐
Blurred Vision?	☐	☐
Severe Anxiety?	☐	☐
Chest Pain?	☐	☐
Abnormal Sweating?	☐	☐

Patient Name: _____

MRN: _____

Study Number: _____

Date/Time of Interview: _____

Questions or Concerns:
Jimin Kim, MD
e: jjkim@bwh.harvard.edu
pg: 38918

Mass General Brigham

Continuing Review Adverse Event Attestation

Principal Investigator:	Jimin Kim, MD
Project Title: **Clinical Trial**	**Second-line Uterotonics in Postpartum Hemorrhage: A Randomized**
Date Completed:	04/05/2022

- PI to complete Adverse Event Attestation at the time of Continuing Review.
- PI/Staff to upload completed attestation to Insight in place of Adverse Event Log with Continuing Review application.

By signing off on this Insight application, PI attests to the following:

X I acknowledge the importance of adverse event tracking as a means of evaluating subject safety.

X I have reviewed the Mass General Brigham policy on Reporting Unanticipated Problems .

X I attest that I/my team are keeping an Adverse Event (AE) Log.

X I have reviewed the AE Log associated with this study and find

X No adverse events have occurred so far during the study period of the trial.

All expected adverse events are recorded on the log and are commensurate with the known risks of the approved study.

Per above policy, all unanticipated problems indicating new or increased risks to subjects (including any unexpected adverse events) have been reported promptly (within 5 business days/7 calendar days of becoming aware) to the IRB and are recorded on the log.

Northwestern | RESEARCH

Northwestern University
Institutional Review Board
Biomedical IRB
750 N. Lake Shore Dr., 7th Fl.
Chicago, Illinois 60611

irb@northwestern.edu
Office 312. 503. 9338

Social & Behavorial Sciences IRB
600 Foster St., 2nd Floor
Evanston, Illinois 60208

sbsirb@northwestern.edu
Office 847. 467. 1723

APPROVAL OF NEW STUDY

DATE: April 12, 2021

TO: Dr. Paloma Toledo
FROM: Office of the IRB

DETERMINATION DATE: 4/12/2021
APPROVAL DATE: 4/2/2021
EXPIRATION DATE: 4/1/2022

The Northwestern University IRB reviewed and approved the submission described below:

Type of Submission:	Initial Study
Review Level:	Committee
Title of Study:	Second Line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial
Principal Investigator:	Paloma Toledo
IRB ID:	STU00214439
Funding Source:	Name: Anesthesiology
Documents Reviewed:	• Local Protocol Amendment 04/07/2021, Category: IRB Protocol; • Carboprost Med Package Insert, Category: Drug Attachment; • Uterine Tone Score, Category: Data Collection Tools; • Brigham Harvard Invitation Letter 03.05.2020, Category: Other; • Partners IRB Brigham Protocol, Category: IRB Protocol; • 2-4 hour Data Collection, Category: Data Collection Tools; • Partners IRB approval 05/27/2020, Category: Approval/Authorization Letter; • 18-24 Hour Data Collection, Category: Data Collection Tools; • Partners IRB approval 10.10.2018, Category: Approval/Authorization Letter; • Methergine Med Package Insert, Category: Drug Attachment; • Consent V 1.0 04/09/2021, Category: Consent Form;
Special Determination(s):	Pregnant women; The panel agreed that the study is no more than minimal risk to pregnant patients, as activities are standard of care.
Clinical Trial:	Yes

In conducting this study, you are required to follow the requirements listed in the Northwestern University (NU) Investigator Manual (HRP-103), which can be found by navigating to the policy section of the IRB website. Additionally, as Principal Investigator (PI) of this research study, you are expected to

adhere to the investigator responsibilities outlined in the "What are my obligations as Investigator in order to conduct Human Research" section of the Investigator Manual (HRP-103).

If your study is a clinical trial, there are additional requirements including trial registration and results reporting on ClinicalTrials.gov. Federally-funded clinical trials are also required to post one IRB approved consent form, used during enrollment, on a publicly available federal website such as ClinicalTrials.gov. Please visit the clinical trials page on the IRB website for more information. If you would like an account created or need other assistance with ClinicalTrials.gov, please email clinicaltrials.gov@northwestern.edu.

If you are unable to complete the study within the approval period, you will need to submit a continuing review to renew the study. The continuing review should be submitted no more than 60 days and no less than 30 days prior to the expiration date.

NU IRB approval does not constitute or guarantee institutional approval and/or support. Investigators and study team members must comply with all applicable federal, state, and local laws, as well as NU Policies and Procedures, which may include obtaining approval for your research activities from other individuals or entities.

For IRB-related questions, please consult the NU IRB website at http://irb.northwestern.edu. For general research questions, please consult the NU Office for Research website at www.research.northwestern.edu.

Additionally, please note that the analyst who you worked with during the initial review and approval of your study is not the analyst that is responsible for the review of any subsequent modifications, continuing reviews, or RNIs. As such, please direct any further questions about modifications, continuing reviews, or RNIs to the analyst assigned to the subsequent submission.

NOVARTIS

Methergine®

(methylergonovine maleate)

Tablets, USP

(methylergonovine maleate)

Injection, USP

Rx only

DESCRIPTION

Methergine® (methylergonovine maleate) is a semisynthetic ergot alkaloid used for the prevention and control of postpartum hemorrhage.

Methergine is available in sterile ampuls of 1 mL, containing 0.2 mg methylergonovine maleate for intramuscular or intravenous injection and in tablets for oral ingestion containing 0.2 mg methylergonovine maleate.

Tablets

Active Ingredient: methylergonovine maleate, USP, 0.2 mg.

Inactive Ingredients: acacia, carnauba wax, D&C Red #7, FD&C Blue #1, gelatin special, lactose, maleic acid, mixed parabens, povidone, sodium benzoate, sodium hydroxide, starch, stearic acid, sucrose, talc, and titanium dioxide.

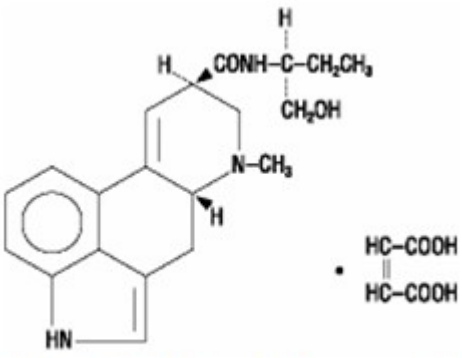
Ampuls: 1 mL, clear, colorless solution.

Active Ingredient: methylergonovine maleate, USP, 0.2 mg.

Inactive Ingredients: maleic acid, 0.10 mg; sodium chloride, 7.0 mg; water for injection, qs to 1 mL.

Chemically, methylergonovine maleate is designated as ergoline8carboxamide, 9,10didehydro*N*[1 (hydroxymethyl)propyl]6methyl, [8ù(*S*)], (*Z*)2butenedioate (1:1) (salt).

Its structural formula is



$C_{20}H_{25}N_3O_2 \bullet C_4H_4O_4$ Mol. wt. – 455.51

CLINICAL PHARMACOLOGY

Methergine (methylergonovine maleate) acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions. Thus, it induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss. The onset of action after I.V. administration is immediate; after I.M. administration, 25 minutes, and after oral administration, 5 10 minutes.

Pharmacokinetic studies following an I.V. injection have shown that methylergonovine is rapidly distributed from plasma to peripheral tissues within 23 minutes or less. The bioavailability after oral administration was reported to be about 60% with no accumulation after repeated doses. During delivery, with intramuscular injection, bioavailability increased to 78%. Ergot alkaloids are mostly eliminated by hepatic metabolism and excretion, and the decrease in bioavailability following oral administration is probably a result of firstpass metabolism in the liver.

Bioavailability studies conducted in fasting healthy female volunteers have shown that oral absorption of a 0.2 mg methylergonovine tablet was fairly rapid with a mean peak plasma concentration of 3243 ± 1308 pg/mL observed at 1.12 ± 0.82 hours. For a 0.2 mg intramuscular injection, a mean peak plasma concentration of 5918 ± 1952 pg/mL was observed at 0.41 ± 0.21 hours. The extent of absorption of the tablet, based upon methylergonovine plasma concentrations, was found to be equivalent to that of the I.M. solution given orally, and the extent of oral absorption of the I.M. solution was proportional to the dose following administration of 0.1, 0.2, and 0.4 mg. When given intramuscularly, the extent of absorption of Methergine solution was about 25% greater than the tablet. The volume of distribution (Vd_{ss}/F) of methylergonovine was calculated to be 56.1 ± 17.0 liters, and the plasma clearance (CLp/F) was calculated to be 14.4 ± 4.5 liters per hour. The plasma level decline was biphasic with a mean elimination halflife of 3.39 hours (range 1.5 to 12.7 hours). A delayed gastrointestinal absorption (T_{max} about 3 hours) of Methergine tablet might be observed in postpartum women during continuous treatment with this oxytocic agent.

INDICATIONS AND USAGE

Following delivery of the placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

CONTRAINDICATIONS

Hypertension; toxemia; pregnancy; and hypersensitivity.

WARNINGS

General

This drug should not be administered I.V. routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If I.V. administration is considered essential as a lifesaving measure, Methergine (methylergonovine maleate) should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intraarterial or periarterial injection should be strictly avoided.

Caution should be exercised in the presence of impaired hepatic or renal function.

Breast-feeding

Mothers should not breastfeed during treatment with Methergine. Milk secreted during this period should be discarded. Methergine may produce adverse effects in the breastfeeding infant. Methergine may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of Methergine before initiating or resuming breast feeding

Coronary artery disease

Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovineinduced vasospasm.

Medication errors

Inadvertent administration of Methergine to newborn infants has been reported. In these cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required.

Methergine has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn . Due to the potential for accidental neonatal exposure, Methergine injection should be stored separately from medications intended for neonatal administration.

PRECAUTIONS

General

Caution should be exercised in the presence of sepsis, obliterative vascular disease. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

Drug Interactions

CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors)

There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there have been no reports of such interactions with methylergonovine alone, potent CYP 3A4 inhibitors should not be coadministered with methylergonovine. Examples of some of the more potent CYP 3A4 inhibitors include macrolide antibiotics (e.g., erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (e.g., ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (e.g., ketoconazole, itraconazole, voriconazole). Less potent CYP 3A4 inhibitors should be administered with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. These lists are not exhaustive, and the prescriber should consider the effects on CYP 3A4 of other agents being considered for concomitant use with methylergonovine.

CYP3A4 inducers

Drugs (e.g. nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methergine.

Beta-blockers

Caution should be exercised when Methergine is used concurrently with betablockers. Concomitant administration with betablockers may enhance the vasoconstrictive action of ergot alkaloids.

Anesthetics

Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of Methergine.

Glyceryl trinitrate and other antianginal drugs

Methylergonovine maleate produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs.

No pharmacokinetic interactions involving other cytochrome P450 isoenzymes are known.

Caution should be exercised when Methergine (methylergonovine maleate) is used concurrently with other vasoconstrictors, ergot alkaloids, or prostaglandins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No longterm studies have been performed in animals to evaluate carcinogenic potential. The effect of the drug on mutagenesis or fertility has not been determined.

Pregnancy

Category C. Animal reproductive studies have not been conducted with Methergine. It is also not known whether methylergonovine maleate can cause fetal harm or can affect reproductive capacity. Use of Methergine is contraindicated during pregnancy because of its uterotonic effects. (See INDICATIONS AND USAGE.)

Labor and Delivery

The uterotonic effect of Methergine is utilized after delivery to assist involution and decrease hemorrhage, shortening the third stage of labor.

Nursing Mothers

Mothers should not breastfeed during treatment with Methergine and at least 12 hours after administration of the last dose. Milk secreted during this period should be discarded.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of Methergine did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most common adverse reaction is hypertension associated in several cases with seizure and/or headache. Hypotension has also been reported. Abdominal pain (caused by uterine contractions), nausea and vomiting have occurred occasionally. Rarely observed reactions have included: acute myocardial infarction, transient chest pains, vasoconstriction, vasospasm, coronary arterial spasm, bradycardia, tachycardia, dyspnea, hematuria, thrombophlebitis, water intoxication, hallucinations, leg cramps, dizziness, tinnitus, nasal congestion, diarrhea, diaphoresis, palpitation, rash, and foul taste.[1]

There have been rare isolated reports of anaphylaxis, without a proven causal relationship to the drug product.

Postmarketing Experience

The following adverse drug reactions have been derived from postmarketing experience with Methergine via spontaneous case reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Nervous system disorders
Cerebrovascular accident, paraesthesia

Cardiac disorders
Ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block

DRUG ABUSE AND DEPENDENCE

Methergine (methylergonovine maleate) has not been associated with drug abuse or dependence of either a physical or psychological nature.

OVERDOSAGE

Symptoms of acute overdose may include: nausea, vomiting, oliquria, abdominal pain, numbness, tingling of the extremities, rise in blood pressure, in severe cases followed by hypotension, respiratory depression, hypothermia, convulsions, and coma.

Because reports of overdosage with Methergine (methylergonovine maleate) are infrequent, the lethal dose in humans has not been established. The oral LD_{50} (in mg/kg) for the mouse is 187, the rat 93, and the rabbit 4.5.[2] Several cases of accidental Methergine injection in newborn infants have been reported, and in such cases 0.2 mg represents an overdose of great magnitude. However, recovery occurred in all but one case following a period of respiratory depression, hypothermia, hypertonicity with jerking movements, and convulsions.

Also, several children 13 years of age have accidentally ingested up to 10 tablets (2 mg) with no apparent ill effects. A postpartum patient took 4 tablets at one time in error and reported paresthesias and clamminess as her only symptoms.

Treatment of acute overdosage is symptomatic and includes the usual procedures of:

1. removal of offending drug by inducing emesis, gastric lavage, catharsis, and supportive diuresis.
2. maintenance of adequate pulmonary ventilation, especially if convulsions or coma develop.
3. correction of hypotension with pressor drugs as needed.
4. control of convulsions with standard anticonvulsant agents.
5. control of peripheral vasospasm with warmth to the extremities if needed.[3]

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Intramuscularly

1 mL, 0.2 mg, after delivery of the anterior shoulder, after delivery of the placenta, or during the puerperium. May be repeated as required, at intervals of 24 hours.

Intravenously

1 mL, 0.2 mg, administered slowly over a period of no less than 60 seconds (See WARNINGS.)

Orally

One tablet, 0.2 mg, 3 or 4 times daily in the puerperium for a maximum of 1 week.

HOW SUPPLIED

Tablets

0.2 mg round, coated, orchid, branded “7854” one side, “SANDOZ” other side.

Bottles of 100……..NDC 0078005405

Ampuls

1 mL size

Boxes of 20…….NDC 0078005303

Store and Dispense

Tablets: Store below 25°C (77°F); in tight, lightresistant container.

Ampuls: Store in refrigerator, 2θC8°C (36°F46°F). Protect from light. Administer only if solution is clear and colorless.

NOVARTIS

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2012June

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

IMPORTANT DRUG WARNING

RE: **MEDICATION ERRORS RELATED TO ACCIDENTAL ADMINISTRATION OF METHERGINE® (methylergonovine maleate) INJECTION IN NEWBORN INFANTS**

June 2012

Dear Healthcare Professional:

Novartis Pharmaceuticals Corporation ("Novartis") would like to inform you about medication errors associated with the accidental administration of Methergine injection in newborn infants. Methergine is used for the prevention andcontrol of postpartum hemorrhage. Serious adverse outcomes that have been reported with inadvertent administration of Methergine to a newborn include **respiratory depression, cyanosis, oliguria, and seizures.** Examples of errors are listed below, [1]

- Methergine injection intended for the mother has been inadvertently administered to the newborn in error.
- Methergine injection intended for the mother has been confused with routine injectable medications intended for the newborns, such as vitamin K injection and Hepatitis B vaccine.

These errors appear to be 1) due to the mother and newborn both being administered medications in the same room and/or 2) because the medications can be stored in similar locations such as a refrigerator attached to an automatic dispensing machine where medications for the mother and newborn are stored together. Therefore, the following recommendations are suggested:

- Methergine injection should be physically separated from other injectable pediatric medications, such as Hepatitis B vaccine and vitamin K. Having separate bins in one refrigerator may not ensure enough separation because there is still a possibility that Methergine injection, Hepatitis B vaccine or other medication could be placed in the wrong bin. Separate refrigerators or automated dispensing machines for the mother and newborn medications may be considered, if feasible.

- Administering medications to newborn in a setting other than in the mother's room. This could be a separate unit where all routine newborn medications are administered or a separate room on the Labor and Delivery unit where routine medications for newborns are administered.

[1] Cases have been reported to FDA, Novartis, and Quantros MedMarx

Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Please note that this presentation of the risk profile for Methergine is not comprehensive. Please refer to the enclosed Methergine full Prescribing Information for a complete discussion of the risks associated with Methergine.

To report adverse events potentially associated with Methergine, please call Novartis Pharmaceuticals Corporation at 1-888-NOW-NOVA (1-888-669-6682).

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

Phone at 1-800-FDA-1088 (1-800-332-1088)
Facsimile at 1-800-FDA-0178 (1-800-332-0178)
Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

Please contact Novartis at 1-888-NOW-NOVA (1-888-669-6682) if you have any questions about Methergine or this information.

Sincerely,

Enclosure: Methergine – Full Prescribing Information

Hemabate®
carboprost tromethamine
injection, USP

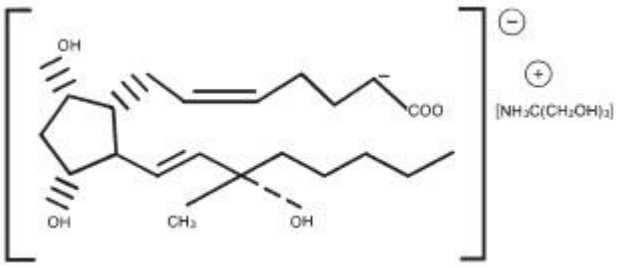
DESCRIPTION

HEMABATE Sterile Solution, an oxytocic, contains the tromethamine salt of the (15S) 15 methyl analogue of naturally occurring prostaglandin F2Į in a solution suitable for intramuscular injection.

Carboprost tromethamine is the established name for the active ingredient in HEMABATE. Four other chemical names are:

1. (15S)15methyl prostaglandin F2Į tromethamine salt
2. 7(3Į,5Įdihydroxy2ß[(3S)3hydroxy3methyl*trans*1octenyl]1Į cyclopentyl]*cis*5heptenoic acid compound with 2amino2(hydroxymethyl) 1,3propanediol
3. (15S)9Į,11Į,15trihydroxy15methylprosta*cis*5, *trans*13dienoic acid tromethamine salt
4. (15S)15methyl PGF2ĮTHAM

The structural formula is represented below:



The molecular formula is $C_{25}H_{47}O_8N$. The molecular weight of carboprost tromethamine is 489.64. It is a white to slightly offwhite crystalline powder. It generally melts between 95° and 105° C, depending on the rate of heating.

Carboprost tromethamine dissolves readily in water at room temperature at a concentration greater than 75 mg/mL.

Each mL of HEMABATE Sterile Solution contains carboprost tromethamine equivalent to 250 mcg of carboprost, 83 mcg tromethamine, 9 mg sodium chloride, and 9.45 mg benzyl alcohol added as preservative. When necessary, pH is adjusted with sodium hydroxide and/or hydrochloric acid. The solution is sterile.

CLINICAL PHARMACOLOGY

Carboprost tromethamine administered intramuscularly stimulates in the gravid uterus myometrial contractions similar to labor contractions at the end of a full term pregnancy. Whether or not these contractions result from a direct effect of carboprost on the

myometrium has not been determined. Nonetheless, they evacuate the products of conception from the uterus in most cases.

Postpartum, the resultant myometrial contractions provide hemostasis at the site of placentation.

Carboprost tromethamine also stimulates the smooth muscle of the human gastrointestinal tract. This activity may produce the vomiting or diarrhea or both that is common when carboprost tromethamine is used to terminate pregnancy and for use postpartum. In laboratory animals and also in humans carboprost tromethamine can elevate body temperature. With the clinical doses of carboprost tromethamine used for the termination of pregnancy, and for use postpartum, some patients do experience transient temperature increases.

In laboratory animals and in humans large doses of carboprost tromethamine can raise blood pressure, probably by contracting the vascular smooth muscle. With the doses of carboprost tromethamine used for terminating pregnancy, this effect has not been clinically significant. In laboratory animals and also in humans carboprost tromethamine can elevate body temperature. With the clinical doses of carboprost tromethamine used for the termination of pregnancy, some patients do experience temperature increases. In some patients, carboprost tromethamine may cause transient bronchoconstriction.

Drug plasma concentrations were determined by radioimmunoassay in peripheral blood samples collected by different investigators from 10 patients undergoing abortion. The patients had been injected intramuscularly with 250 micrograms of carboprost at two hour intervals. Blood levels of drug peaked at an average of 2060 picograms/mL onehalf hour after the first injection then declined to an average concentration of 770 picograms/mL two hours after the first injection just before the second injection. The average plasma concentration onehalf hour after the second injection was slightly higher (2663 picograms/mL) than that after the first injection and decreased again to an average of 1047 picograms/mL by two hours after the second injection. Plasma samples were collected from 5 of these 10 patients following additional injections of the prostaglandin. The average peak concentrations of drug were slightly higher following each successive injection of the prostaglandin, but always decreased to levels less than the preceding peak values by two hours after each injection.

Five women who had delivery spontaneously at term were treated immediately postpartum with a single injection of 250 micrograms of carboprost tromethamine. Peripheral blood samples were collected at several times during the four hours following treatment and carboprost tromethamine levels were determined by radioimmunoassay. The highest concentration of carboprost tromethamine was observed at 15 minutes in two patients (3009 and 2916 picograms/mL), at 30 minutes in two patients (3097 and 2792 picograms/mL), and at 60 minutes in one patient (2718 picograms/mL).

INDICATIONS AND USAGE

HEMABATE Sterile Solution is indicated for aborting pregnancy between the 13th and 20th weeks of gestation as calculated from the first day of the last normal menstrual period and in the following conditions related to second trimester abortion:

1. Failure of expulsion of the fetus during the course of treatment by another method;
2. Premature rupture of membranes in intrauterine methods with loss of drug and insufficient or absent uterine activity;
3. Requirement of a repeat intrauterine instillation of drug for expulsion of the fetus;
4. Inadvertent or spontaneous rupture of membranes in the presence of a previable fetus and absence of adequate activity for expulsion.

HEMABATE is indicated for the treatment of postpartum hemorrhage due to uterine atony which has not responded to conventional methods of management. Prior treatment should include the use of intravenously administered oxytocin, manipulative techniques such as uterine massage and, unless contraindicated, intramuscular ergot preparations. Studies have shown that in such cases, the use of HEMABATE has resulted in satisfactory control of hemorrhage, although it is unclear whether or not ongoing or delayed effects of previously administered ecbolic agents have contributed to the outcome. In a high proportion of cases, HEMABATE used in this manner has resulted in the cessation of life threatening bleeding and the avoidance of emergency surgical intervention.

CONTRAINDICATIONS

1. Hypersensitivity (including anaphylaxis and angioedema) to HEMABATE Sterile Solution [*see ADVERSE REACTIONS, Post-marketing Experience*]
2. Acute pelvic inflammatory disease
3. Patients with active cardiac, pulmonary, renal or hepatic disease

WARNINGS

HEMABATE Sterile Solution (carboprost tromethamine), like other potent oxytocic agents, should be used only with strict adherence to recommended dosages. HEMABATE should be used by medically trained personnel in a hospital which can provide immediate intensive care and acute surgical facilities.

HEMABATE does not appear to directly affect the fetoplacental unit. Therefore, the possibility does exist that the previable fetus aborted by HEMABATE could exhibit transient life signs. HEMABATE is not indicated if the fetus *in utero* has reached the stage of viability. HEMABATE should not be considered a feticidal agent.

Evidence from animal studies has suggested that certain other prostaglandins have some teratogenic potential. Although these studies do not indicate that HEMABATE is

teratogenic, any pregnancy termination with HEMABATE that fails should be completed by some other means.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

PRECAUTIONS

General

Animal studies lasting several weeks at high doses have shown that prostaglandins of the E and F series can induce proliferation of bone. Such effects have also been noted in newborn infants who have received prostaglandin E1 during prolonged treatment. There is no evidence that short term administration of HEMABATE Sterile Solution can cause similar bone effects.

In patients with a history of asthma, hypo or hypertension, cardiovascular, renal, or hepatic disease, anemia, jaundice, diabetes, or epilepsy, HEMABATE should be used cautiously.

As with any oxytocic agent, HEMABATE should be used with caution in patients with compromised (scarred) uteri.

Abortion

As with spontaneous abortion, a process which is sometimes incomplete, abortion induced by HEMABATE may be expected to be incomplete in about 20% of cases.

Although the incidence of cervical trauma is extremely small, the cervix should always be carefully examined immediately postabortion.

Use of HEMABATE is associated with transient pyrexia that may be due to its effect on hypothalamic thermoregulation. Temperature elevations exceeding 2° F (1.1° C) were observed in approximately oneeighth of the patients who received the recommended dosage regimen. In all cases, temperature returned to normal when therapy ended. Differentiation of postabortion endometritis from druginduced temperature elevations is difficult, but with increasing clinical experience, the distinctions become more obvious and are summarized below:

	Endometritis pyrexia	**Pyrexia induced by HEMABATE**
1.	**Time of onset:** Typically, on third post abortional day (38° C or higher).	Within 1 to 16 hours after the first injection.
2.	**Duration:** Untreated pyrexia and infection continue and may give rise to other pelvic infections.	Temperatures revert to pretreatment levels after discontinuation of therapy without any other treatment.
3.	**Retention:** Products of conception are often retained in the cervical os or uterine cavity.	Temperature elevation occurs whether or not tissue is retained.

4.	**Histology:** Endometrium is infiltrated with lymphocytes and some areas are necrotic and hemorrhagic.	Although the endometrial stroma may be edematous and vascular, it is not inflamed.
5.	**The uterus:** Often remains boggy and soft with tenderness over the fundus, and pain on moving the cervix on bimanual examination.	Uterine involution normal and uterus is not tender.
6.	**Discharge:** Often associated with foul smelling lochia and leukorrhea.	Lochia normal.

7. **Cervical culture:** The culture of pathological organisms from the cervix or uterine cavity after abortion alone does not warrant the diagnosis of septic abortion in the absence of clinical evidence of sepsis. Pathogens have been cultured soon after abortion in patients with no infections. Persistent positive culture with clear clinical signs of infections are significant in the differential diagnosis.
8. **Blood count:** Leukocytosis and differential white cell counts do not distinguish between endometritis and hyperthermia caused by HEMABATE since total WBC's may increase during infection and transient leukocytosis may also be druginduced.

   Fluids should be forced in patients with druginduced fever and no clinical or bacteriological evidence of intrauterine infection. Any other simple empirical measures for temperature reduction are unnecessary because all fevers induced by HEMABATE have been transient or selflimiting.

Postpartum Hemorrhage

Increased blood pressure. In the postpartum hemorrhage series, 5/115 (4%) of patients had an increase of blood pressure reported as a side effect. The degree of hypertension was moderate and it is not certain as to whether this was in fact due to a direct effect of HEMABATE or a return to a status of pregnancy associated hypertension manifest by the correction of hypovolemic shock. In any event the cases reported did not require specific therapy for the elevated blood pressure.

Use in patients with chorioamnionitis. During the clinical trials with HEMABATE, chorioamnionitis was identified as a complication contributing to postpartum uterine atony and hemorrhage in 8/115 (7%) of cases, 3 of which failed to respond to HEMABATE. This complication during labor may have an inhibitory effect on the uterine response to HEMABATE similar to what has been reported for other oxytocic agents.[1]

Drug Interactions

HEMABATE may augment the activity of other oxytocic agents. Concomitant use with other oxytocic agents is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic bioassay studies have not been conducted in animals with HEMABATE due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.

Pregnancy: Teratogenic Effects: *Pregnancy Category C*
Animal studies do not indicate that HEMABATE is teratogenic, however, it has been shown to be embryotoxic in rats and rabbits and any dose which produces increased uterine tone could put the embryo or fetus at risk.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
The adverse effects of HEMABATE Sterile Solution are generally transient and reversible when therapy ends. The most frequent adverse reactions observed are related to its contractile effect on smooth muscle.

In patients studied, approximately twothirds experienced vomiting and diarrhea, approximately onethird had nausea, oneeighth had a temperature increase greater than 2° F, and onefourteenth experienced flushing.

The pretreatment or concurrent administration of antiemetic and antidiarrheal drugs decreases considerably the very high incidence of gastrointestinal effects common with all prostaglandins used for abortion. Their use should be considered an integral part of the management of patients undergoing abortion with HEMABATE.

Of those patients experiencing a temperature elevation, approximately onesixteenth had a clinical diagnosis of endometritis. The remaining temperature elevations returned to normal within several hours after the last injection.

Adverse effects observed during the use of HEMABATE for abortion and for hemorrhage, not all of which are clearly drug related, in decreasing order of frequency include:

Vomiting
Diarrhea
Nausea
Flushing or hot flashes
Chills or shivering
Coughing
Headaches
Endometritis
Hiccough
Dysmenorrhealike pain
Paresthesia
Backache
Muscular pain
Breast tenderness
Nervousness
Nosebleed
Sleep disorders
Dyspnea
Tightness in chest
Wheezing
Posterior cervical perforation
Weakness
Diaphoresis
Dizziness
Blurred vision
Epigastric pain
Excessive thirst
Twitching eyelids

Eye pain
Drowsiness
Dystonia
Asthma
Injection site pain
Tinnitus
Vertigo
Vasovagal syndrome
Dryness of mouth
Hyperventilation
Respiratory distress
Hematemesis
Taste alterations
Urinary tract infection
Septic shock
Torticollis
Lethargy
Hypertension
Tachycardia
Pulmonary edema
Endometritis from IUCD
Gagging, retching
Dry throat
Sensation of choking
Thyroid storm
Syncope
Palpitations
Rash
Upper respiratory infection
Leg cramps
Perforated uterus
Anxiety
Chest pain
Retained placental fragment
Shortness of breath
Fullness of throat
Uterine sacculation
Faintness, light headedness
Uterine rupture

The most common complications when HEMABATE was utilized for abortion requiring additional treatment after discharge from the hospital were endometritis, retained placental fragments, and excessive uterine bleeding, occurring in about one in every 50 patients.

Postmarketing experience:

Hypersensitivity reactions (e.g. Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Angioedema).

DOSAGE AND ADMINISTRATION

1. Abortion and Indications 1–4

An initial dose of 1 mL of HEMABATE Sterile Solution (containing the equivalent of 250 micrograms of carboprost) is to be administered deep in the muscle with a tuberculin syringe. Subsequent doses of 250 micrograms should be administered at 1½ to 3½ hour intervals depending on uterine response.

An optional test dose of 100 micrograms (0.4 mL) may be administered initially. The dose may be increased to 500 micrograms (2 mL) if uterine contractility is judged to be inadequate after several doses of 250 micrograms (1 mL).

The total dose administered of carboprost tromethamine should not exceed 12 milligrams and continuous administration of the drug for more than two days is not recommended.

2. For Refractory Postpartum Uterine Bleeding:

An initial dose of 250 micrograms of HEMABATE Sterile Solution (1 mL of HEMABATE) is to be given deep, intramuscularly. In clinical trials it was found that the majority of successful cases (73%) responded to single injections. In some selected cases, however, multiple dosing at intervals of 15 to 90 minutes was carried out with successful outcome. The need for additional injections and the interval at which these should be given can be determined only by the attending physicians as dictated by the course of clinical events. The total dose of HEMABATE should not exceed 2 milligrams (8 doses).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

HEMABATE Sterile Solution is available in the following packages:

1 mL ampoules	NDC 0009085605
10 x 1 mL ampoules	NDC 0009085608

Each mL of HEMABATE contains carboprost tromethamine equivalent to 250 mcg of carboprost.

HEMABATE must be refrigerated at 2° to 8° C (36° to 46° F).

[1]Duff, Sanders, and Gibbs; The course of labor in term patients with chorioamnionitis; *Am. J. Obstet. Gynecol.;* vol. 147, no. 4, October 15, 1983 pp 391–395.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com

Rx only

LAB00325.0
Revised December 2013

PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Jimin Kim, MD

PROTOCOL TITLE
Second-line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial

FUNDING
n.a.

VERSION DATE
04/19/2022

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

The purpose of this study is to prospectively compare the efficacy of the two most commonly used second-line uterotonic agents in postpartum hemorrhage (PPH): methylergonovine maleate (methylergonovine) and 15-methyl prostaglandin F2α (carboprost). Study participants with abnormal bleeding immediately post-cesarean delivery will receive, upon request, methergine and/or carboprost in a randomized fashion after oxytocin. The choice of carboprost or methylergonovine as the first additional uterotonic to be administered will be randomized and all members of the care team will be blinded to the randomization. Dosing and timing of the uterotonics will be unaltered from standard of care. Uterine tone score, blood loss, need for additional uterotonics, need for transfusion and interventions to control bleeding will be recorded. We hypothesize that patients receiving methylergonovine will have a 1-point greater reduction in uterine tone (on a 0-10 scale) at 10 minutes after administration compared to carboprost.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Primary PPH is defined by the American College of Obstetricians and Gynecologists as a cumulative blood loss >1000 mL or blood loss

accompanied by signs of hypovolemia within 24 hours of delivery. It remains the leading source of maternal morbidity and mortality worldwide with uterine atony identified as the underlying cause in up to 80% of cases [Combs et al. Obstet Gynecol 1991;77:69–76. Dildy GA. Clin Obstet Gynecol. 2002; 45(2): 330-44]. Oxytocin is routinely administered prophylactically during the third stage of labor to decrease the risk of PPH [Westhoff et al. Cochrane Database Syst Rev 2013; 10:CD001808], and it is considered the first-line medical treatment for PPH. When postpartum bleeding persists, a multidisciplinary approach combining mechanical, pharmacologic, and surgical measures is indicated. The most effective second-line uterotonic agent remains unknown and a lack of consensus exists regarding the best pharmacologic management of PPH.

Recent literature indicates that methylergonovine may be superior to carboprost in the treatment of PPH [Butwick et al. AJOG 2015], but due to the unpredictable and emergent nature of PPH, high quality evidence of their comparative efficacy is scarce. This study will be the first to prospectively compare the two agents in a randomized fashion thereby allowing for direct comparison of their efficacy.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

The study will be conducted as a randomized, double blinded prospective trial. All patients of participating obstetricians will initially be given a standard information packet from their obstetrician's office at their 28-week visit. The packet will contain basic information regarding their delivery as well as a copy of the study Consent Form and a Flier outlining this study's goals and methods. Patients meeting eligibility criteria who plan vaginal or cesarean delivery and have reach 37 weeks gestation or greater, will be asked by their obstetrician for permission to be contacted by a study co-investigator by email. Those patients who are willing to be contacted will be sent an email reminding them of the study with a copy of the Study Flier and Consent Form attached to the email.

Eligibility criteria will include all female patients ages 18-50 with delivery of a viable fetus (24 weeks gestation or above) by non-emergent cesarean section (C/S) who experience abnormal immediate postpartum bleeding.

Exclusion criteria for enrollment in the study will include non-English speaking patients requiring an interpreter who are undergoing urgent, non-

scheduled C/S, patients with pre-existing systemic hypertension (HTN) or any hypertensive disorder of pregnancy, patients with cardiovascular disease, patients with asthma, patients who refuse to accept blood transfusion (e.g. Jehovah's Witnesses), patients with a known coagulopathy or abnormal baseline coagulation profile, patients with known or suspected hypersensitivity to either of the two study drugs, and patients with known or suspected delayed PPH after leaving the operating room from the cesarean delivery.

We anticipate enrolling 1250 patients in order to randomizing a total of 100 patients for this study, based on a calculation for 80% power to detect a mean difference of uterine tone score as small as 1.2 using a two-tailed two-sample t test, assuming a standard deviation of 1.9 and significant level at 0.05.

Patients will be recruited from those who deliver by cesarean section at the Brigham and Women's Hospital.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Parturients will be assessed for eligibility using a pre-screening questionnaire at the time of admission to the Labor and Delivery (L&D) unit. Eligible patients will be given the opportunity to consent to participate in the study at the time of admission to the labor and delivery unit, or at the time of consent for elective cesarean section. Emergent cesarean section deliveries will be excluded.

Participants will receive standard care in terms of all medical and surgical interventions to manage postpartum bleeding. This will include a standard infusion of oxytocin immediately postpartum. If a second-line uterotonic is requested after oxytocin, the patient will be randomized by the anesthesiologist to either the "methylergonovine" or "carboprost" study group using a computer-generated randomization scheme printed on a piece of paper (called the Randomization sheet) in a sealed envelope. The anesthesiologist will document the patient MRN and study ID number on this Randomization Sheet and then return it to the envelope. The envelope will also contain a Uterine Tone Score Intraop Data Collection Sheet for documentation of the primary outcome as well as additional information, as described below.

Participants will receive either methylergonovine or carboprost depending on their randomization. The anesthesiologist will withdraw the appointed

medication (based on subject randomization) from the O.R. omnicell and administer it without revealing to anyone in the O.R. which drug was given. They will document the medication in the subject's Epic record in the usual fashion. Obstetricians and nursing staff are not able to view the Epic anesthesia record in real time, and therefore will not be able to see which medication was given by the anesthesiologist. Every effort will be made to avoid having the physician co-investigator be involved in the patient's care. Occasionally, though, if staffing is limited or there is high clinical acuity in the subject's case (e.g. massive postpartum hemorrhage), the anesthesiologist co-investigator who consented the patient may need to be involved in helping with the patient's intraoperative care. If this is the case, coercion will be avoided since the patient consent will occur first, and the study investigator will only become the patient's physician after the informed consenting process is complete. Patients, obstetricians, study co-investigators and nurses will be blinded to the study group assignment but the anesthesiologist will be unblinded to study randomization and the identity of each drug being given.

At the time of administration of the first study drug, the anesthesiologist will ask the obstetrician to rate the uterine tone on a scale of 0 to 10 (0 being 'no tone', 10 being 'excellent tone'). The anesthesiologist will then set a timer. After administration of the study drug, patients will receive our usual standard of care. At 5 minutes and again at 10 minutes from the onset of timing, the anesthesiologist will once again ask the obstetrician for a rating of uterine tone between 0 and 10. These values will be recorded by the anesthesiologist on the Uterine Tone Score Intraop Data Collection sheet provided in the envelope with the Randomization sheet by the investigator.

If a third uterotonic is desired (after oxytocin and the initial study drug), the patient will receive the alternate drug (methylergonovine or carboprost), prepared by the unblinded anesthesiologist. Any additional measures for postpartum bleeding will be provided in the usual fashion as standard of care.

At the end of the C/S, the anesthesiologist will return the Randomization sheet and the Uterine Tone Score Intraop Data Collection sheet in the previously sealed envelope to a folder where all paper documents for the study are temporarily stored in a locked room on the L&D floor. On each day of subject enrollment, the unblinded principal investigator will collect the envelope with the Randomization sheet and Uterine Tone Score Intraop Data Collection sheet and transfer it to a locked filing cabinet in a locked office to which only the principal investigator has access.

After the subject has recovered on the L&D floor and is ready for transfer to the postpartum floor, a blinded study co-investigator will interview the patient by phone (to limit physical contact, due to COVID-19 precautions)

using the '2-4 Hour Interview Guide'. At 18-24 hours postpartum, the subject will again be interviewed by phone by a blinded study co-investigator, using the '18-24 Hour Interview Guide'. Both postpartum interview guides will contain the same content, allowing for subjective adverse effects to be accurately assessed at 2 timepoints. (no later than 24 hours after delivery). This data will be documented on the 2-4 Hour and 18-24 Hour Interview Guides, to be retrieved by the principal investigator (who is not blinded) after the day of subject enrollment, then stored in the locked office, and ultimately entered into a secure electronic database, REDCap, by a blinded study investigator. This will allow them to assess for any subjective side effects of the study medication, as listed below (Secondary Endpoint #9).

An unblinded study investigator not involved in data collection and with access to REDCap will be responsible for collecting all primary and secondary outcomes (including side-effects of study medications) from the Uterine Tone Score Intraop Data Collection sheet, the Pre Transfer Interview Guide and Epic medical records onto the Second Line Uterotonics Data Collection Sheet and entering this information into REDCap. Subject randomization, patient MRN and the linked study ID number will be documented on a separate form in the REDCap database by the unblinded principal investigator, to preserve the integrity of the data collection and entry.

Study endpoints will be:

Primary Endpoint

1. Uterine tone score as recorded at 10 minutes following the administration of the second-line uterotonic.

Secondary Endpoints

1. Uterine tone score recorded at 5 minutes following the administration of the second-line uterotonic.
2. Need for an additional uterotonic agent after the study drug
3. Number of units of blood products transfused (t_0 = time of delivery; t_{final} = 24 hours after delivery)
4. Need for a surgical or radiologic intervention to control bleeding
5. Quantitative intrapartum blood loss
6. Pre- vs post-delivery hematocrit values
7. Maternal morbidity: vasopressor requirement or hypovolemic shock, admission to the intensive care unit postpartum, mechanical ventilation, hypertensive emergency, myocardial ischemia, acute kidney injury, acute lung injury or circulatory overloard from blood transfusion, allergic reaction deemed the result of blood transfusion, hypovolemic shock, or vasopressor requirement.
8. Length of postoperative hospital stay

9. Medication side effects within 2 hrs postpartum: nausea, vomiting or diarrhea, abdominal pain, shortness of breath, headache, blurred vision, anxiety, chest pain, sweating, palpitations

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

All patients undergoing a C/S delivery at the Brigham and Women's Hospital (BWH) have a peripheral IV and baseline laboratory work on admission to the labor and delivery floor. The standard of care at BWH for women undergoing C/S includes spinal anesthesia with bupivacaine, fentanyl, and morphine, as will be used in this study unless contraindicated. The overall anesthetic management of a patient in the operating room will be at the discretion of the anesthesia attending physician, including crystalloid fluid administered, anti-emetic medication, analgesic medication and vasopressors used. Blood products transfused will be at the discretion of the attending physicians.

At the time of C/S and clamping of the umbilical cord, a standard infusion of oxytocin 30U/500mL is begun at a rate of 15-30U/hr. If uterine tone is perceived to be inadequate, this rate may be increased and the obstetrician may attempt maneouvers to improve uterine tone. Additionally, at this time a second-line uterotonic is typically requested.

The choice of whether to give methylergonovine or carboprost as a second-line uterotonic depends primarily on provider preference and the presence of any medical contraindications. Methylergonovine must be avoided in patients at risk for hypertension; carboprost should be avoided in those with current reactive airway disease. If the second-line agent is unsuccessful in curbing the bleeding, the alternate agent is given. Carboprost may be re-administered as often as every 15 minutes; methylergonovine every 4 hours.

Further escalation in treatment involves medical and surgical measures, such as cytotec (misoprostol), intrauterine vasopressin injection, uterine massage, intrauterine balloon tamponade, occlusion of pelvic arteries, B-lynch sutures, or hysterectomy. In this study, patients will have the opportunity to receive one or both of the second-line agents, as well as all other standard measures for PPH management; however the choice of uterotonic that is given first will be randomized.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

This study is designed as a double blinded, randomized study.

Several national and international guidelines have recommended both drugs as second-line uterotonics to treat PPH, but there is no evidence to specify which should be used first, or which might be more effective. Therefore, by giving the patients the opportunity to receive both drugs, any deviation from standard practice and risk to the patients will be minimized.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

All participants will be under the direct care of an obstetric anesthesiologist, obstetrician, and a labor and delivery nurse throughout the course of the study. Standard care will be employed for every patient with the exception of the randomization of the order in which they receive their second-line uterotonic agents. At all times, providers' clinical assessment of the patient will be paramount in guiding decision-making. Providers will have full ability to exercise their best judgement in taking care of the patient. If this results in a decision to deviate from the study protocol, the patient will be cared for according to the providers' discretion. If the practice deviates from the study protocol, the patient will be withdrawn from the study thereafter.

Patients will be monitored carefully by their anesthesia and obstetric providers for any potential side-effects of the medications they receive in the study.

The principal investigator will additionally review all data collection and recruitment on every 5th patient recruited and immediately as needed if a concern arises. At the time of each review point, the principal investigator will review all forms and data entry to ensure completeness, accuracy, and adherence to the protocol. Any concern for adverse events will result in immediate review by the principal investigator with the study being temporarily halted, and the events will be reported to the IRB and the PHRC in accordance with the PHRC Policy on Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events. The principal investigator will be primarily responsible for deciding if the study needs to be stopped, but this can also be decided by any of the study co-investigators.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

As described above, all patients will be treated with the standard of care and should therefore not be exposed to any additional risk or discomfort. As is typical practice, all patients will receive an intravenous (IV) line and baseline labs on admission to the L&D floor, and oxytocin will be given immediately after the baby is delivered and the cord clamped. Thereafter, patients will receive all usual measures to manage postpartum bleeding, including, but not limited to, administration of additional uterotonics, uterine massage, additional diagnostic lab values and resuscitative measures. Second-line uterotonics will be given as per study protocol, with additional uterotonics as per clinical assessment.

After the delivery, the patient will be monitored on the labor and delivery floor for several hours postoperatively before discharge to the postpartum recovery unit, as is customary.

Only clinical providers will be involved in the care of the patient. Study staff will be involved in consent and collection of data points during enrollment, but they will not participate directly in patient care. Privacy and confidentiality will be maintained as per HIPAA standards.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

The incidence of PPH is on the rise in the U.S.A., with uterine atony the main etiology. Oxytocin is given prophylactically in cesarean section deliveries, but when it is inadequate, second-line agents are required. While recent literature suggests methylergonovine may be more effective than carboprost for PPH treatment, no prospective data exists comparing the two. This study may yield new information demonstrating the comparative efficacy of these two drugs. This could guide future practice in determining which second-line agent is preferred for PPH management. In turn, this could allow future

patients to benefit from decreased morbidity and mortality associated with hemorrhage and transfusion.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

All English-speaking patients undergoing non-emergent urgent C/S at the Brigham and Women's Hospital and all English or non-English speaking patients undergoing scheduled C/S will be eligible for participation except those with a known coagulopathy or high risk for coagulopathy (as this might alter the management of bleeding beyond standard measures) as well as those with contraindications to either study drug, i.e. HTN or active asthma (with use of a bronchodilator in the past 24 months) or documented allergy to either drug. Patients refusing to receive blood products due to religious beliefs will also be excluded.

Patients experiencing uterine atony requiring an additional, second-line uterotonic agent after C/S will be randomized to participate in this study, as a result, those who participate will be of the same population that will benefit from this research.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Non-English speaking patients who are undergoing unscheduled, urgent C/S will not be enrolled due to the potentially stressful or urgent nature of all C/S in patients who have failed to deliver in labor. In such cases, there may not be time to adequately obtain informed consent for participation in the study without hindering clinical care. Therefore the study will only enroll urgent C/S patients who speak English and are able to provide informed consent without the aid of an interpreter. Patients undergoing routine, schedule C/S may be English-speaking or non-English speaking, since there will be no undue stress involved preoperatively and there will be ample opportunity for full consent in the patient's first language with the aid of an official in-person interpreter.

For guidance, refer to the following Partners policy:

Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Eligible patients undergoing a scheduled C/S or non-emergent C/S after labor will be provided with the study Flier regarding the study and the study consent form by a study physician investigator or research assistant when they are admitted to the L&D floor. The person will not be directly involved in the care of the patient. Patients will only be approached in their rooms by a study physician to obtain their informed consent. The study physician will follow all institutional policies and contact isolation level safety procedures to minimize risks to the patient of possible COVID-19 exposure. They will maintain a 6-foot distance from the patient as much as possible. There will be minimal shared points of contact between study staff and patient, (such as the consent form, clipboard, or pen). Proper hand hygiene and replacement of PPE will be performed throughout as necessary.

At this time, patients will have the opportunity to ask any questions they may have regarding the study and to opt in or out as desired through conversation with the physician study investigator. During this conversation, the purpose of the study and scope of participation will be discussed. If the patient is agreeable to participation, written consent will be obtained by the physician study investigator. If the patient is non-English speaking, the services of an in-person interpreter will be obtained for the conversation with the study investigator.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

No remuneration will be provided for participation in this study.

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects

https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

All pregnant women receiving care from participating obstetricians will receive an initial informational study Flier and consent form in their 28-wk prenatal information package from the obstetrician's office.

Upon admission to the L&D unit, all potentially eligible patients will be pre-screened using the OB Pre-Screen Questionnaire for 2nd Line Uterotonics Study. Those who meet eligibility criteria will, once again, receive the study Flier and consent form. A physician study investigator who is not involved in their care at the time of consent will review and discuss the study plan at this time, allowing subjects the opportunity to ask questions and address any of their concerns or any issues surrounding the study. Subjects interested in participating will then be consented by the physician investigator and enrolled in the study. An official in-person interpreter fluent in the patient's native language will be used to translate an oral version of the English consent form in the patient's native language. Social distancing will be maintained during all in-person conversations and appropriate PPE will be worn by any staff during these conversations. The patient will be allowed to keep the pen they use to sign the consent form, in order to minimize sharing of physical items, and lower the risk for COVID-19 transmission.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

The principal investigator will be responsible for reviewing the study data after each 5th enrolled patient. The purpose of these reviews will be to identify and correct any potentially unsafe practice or result occurring among the study population. This includes specifically any delay in uterotonic administration, lack of an appropriate uterotonic being administered, or the use of a uterotonic in a patient with a contraindication to that drug.

Any adverse events identified by the principal investigator, or any of the other study investigators, will be reported to the PHRC in accordance with the PHRC Policy on Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

Upon review at the end of each of 5 patients recruited, the principal investigator will note specific frequency of minor and serious adverse events experienced by subjects. Any incidence of frequent minor events or any single serious adverse event will trigger a report generated for submission to the Partners IRB. For any serious concern, the Principal Investigator will halt the study until further discussion with the IRB.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

All physician co-investigators involved in this study will be well informed of recruitment procedures, location of study medications storage, appropriate handling of medications and timing of administration, as well as other protocol details.

The principal investigator will conduct a review of source documentation after every 5 enrolled patients, weekly, or immediately upon recognition of any adverse event. The principal investigator will ensure that the study protocol is conducted in accordance to the final approved IRB. This includes ensuring that recruited patients meet eligibility criteria and are provided with study information in advance of enrollment; reviewing consent documentation and reviewing collected data to ensure that all items are completed, including complications and potential adverse events, and that the data is free of patient identifiers; and following-up on any reported concerns from patients, study staff, or clinicians.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All data related to this study will be treated as confidential. Email communication to potential subjects at term gestation will be sent securely, in accordance with MGB Information Security guidelines. Collected data will be consolidated and entered directly in a de-identified fashion into a secure electronic capture tool, REDCap. Patient MRNs will be the only patient identifier recorded in REDCap; these will be entered with study group allocation and study ID number separately from the other study data into a secure document on REDCap by the unblinded principal investigator. The MRNs will be linked to study information on the randomization sheets, which will be viewed only by the unblinded principal investigator and stored in a locked filing cabinet in a locked office, accessible only by the principal investigator. Any other paper documentation related to study patients and containing patient identifiers will be maintained in the same locked filing cabinet, accessible only by the principal investigator.

Only the principal investigator, and one unblinded co-investigator will have access to the REDCap files. No one other than the study investigators will have any knowledge of the details of the patient's study information, and this data will never be circulated electronically or in any other format.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

No specimens or data will be collected or sent to research collaborators outside Partners or participating sites.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Not applicable to this study.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

No specimens will be collected from outside Partners or any participating sites.

Dear Ms. xxx,

We would like to tell you about an important ongoing study at the Brigham and Women's Hospital that you may be eligible for during your delivery. Your obstetrician, Dr. xxx, is aware and supportive of this research, and mentioned that you agreed to be contacted by the study team.

The study compares two medications (methylergovonive and carboprost) that are used commonly every day to help the uterus contract after birth, but no one knows which one is better. This will be the first study to compare them head to head to decide if one is more effective than the other. We are attaching a study flier and sample consent form here for more information, and we will approach you when you are admitted to Labor & Delivery, in case you would like to participate.

If you would like to learn more about the study, please contact the Principal Investigator, Dr Jimin Kim at jjkim@bwh.harvard.edu. No action is required on your part otherwise.

Thank you for your consideration and we wish you a safe and happy birth experience!

Sincerely,

The investigators of the Second-Line Uterotonics Study.