PART 1: Administrative Details	
Full Study Title	Randomised Controlled Trial: Intrauterine Misoprostol versus Sublingual Misoprostol in the Prevention of Postpartum Hemorrhage at Elective Caesarean Section at Korle Bu Teaching Hospital, Ghana.
Short title (if available)	IUMO
Protocol/ Document Number	Version 2.0
Date of Receipt of the Application	25/05/2023
Phase of Study	2
Study Registration Details	**PACTR202309644870215** Clinical trial approval certificate no. **FDA/CT/241**
Name and Address of Applicant(s)	Dr. Chidinma Peace Ohachenu Korle Bu Teaching Hospital Department of Obstetrics and Gynaecology P.O. Box 77 KBTH Accra-Ghana
Name and Address of Sponsor(s)	(Investigator-led) Dr. Chidinma Peace Ohachenu Korle Bu Teaching Hospital Department of Obstetrics and Gynaecology P.O. Box 77 KBTH Accra-Ghana (Supervisor) Prof. Kobinah Nkyekyer
Name and Address of Principal Investigator(s)	Dr. Chidinma Peace Ohachenu Korle Bu Teaching Hospital Department of Obstetrics and Gynaecology P.O. Box 77 KBTH Accra-Ghana
Study Sites	Korle Bu Teaching Hospital
Study Duration	3 months
FAPAR Number	FDA/CT/PAR/241

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	1. Cytotec (Misoprostol) 200 mcg tablets 2. Promptin 10 (Oxytocin) 5IU
Justification of Investigational Product(s) including comparators	The study highlights the effectiveness of intrauterine misoprostol administration for reducing postpartum hemorrhage (PPH), particularly due to uterine atony. Lower doses may offer a balance between efficacy and minimizing side effects and costs compared to higher doses. The findings suggest that further multicenter studies could support the adoption of lower-dose intrauterine misoprostol, potentially reducing morbidity and mortality associated with PPH. Additionally, the study contributes to the limited literature on this subject, serving as a model for similar research in Ghana and beyond.

PART 3: Study Summary

Study Objectives

Primary

- To evaluate the effectiveness of intrauterine misoprostol compared to sublingual misoprostol in the prevention of postpartum haemorrhage among women undergoing elective caesarean section in Korle-Bu Teaching hospital.

Secondary

- To compare the blood loss after delivery of placenta to 3 hours post-delivery (overall blood loss) between women who received 400mcg intrauterine misoprostol plus 5IU IV oxytocin and those who received 600mcg sublingual misoprostol plus 5IU IV oxytocin.
- To compare the pre-operative and 24-hour post-operative haematocrit levels between women who received 400mcg intrauterine misoprostol plus 5IU IV oxytocin and those who received 600mcg sublingual misoprostol plus 5IU IV oxytocin.
- To compare the need for additional PPH interventions (additional uterotonics, blood transfusion, uterine tamponade, compression sutures, artery ligation, hysterectomy, relaparotomy and admission to ICU) applied in the first 24 hours following delivery between women who received 400mcg intrauterine misoprostol plus 5IU IV oxytocin and those who received 600mcg sublingual misoprostol plus 5IU IV oxytocin.

PART 3: Study Summary

- To compare the side effects profile of 400mcg intrauterine misoprostol plus 5IU IV oxytocin with that of 600mcg sublingual misoprostol plus 5IU IV oxytocin in the first 3 hours following administration.

Study Design

- This study is a single-blind equivalence randomized controlled trial among women undergoing elective caesarean section in Korle Bu Teaching Hospital. Participants randomised to the study group will receive 400mcg tablets of intrauterine misoprostol (after delivery of the placenta and before uterine incision repair) plus 5IU IV oxytocin, while those randomised to the control group will receive 600mcg of sublingual misoprostol plus 5IU IV oxytocin. A data collection tool (proforma) will be used to obtain participants' biodata, and preoperative, intraoperative, and postoperative data, and side-effect profile.

- Blood loss will be assessed by a combined method: clinical assessment (measurement of the intraoperative blood loss from the time of delivery placenta to end of surgery), gravimetric assessment (weighing of vulval pads, and bed mats used in the first three hours following elective caesarean section), and laboratory assessment of primary postpartum haemorrhage through a change of ≥10% between preoperative haematocrit (Hct) and 24hr postoperative Hct.

Eligibility Criteria

Women who meet the following criteria will be included in the study;

- 18 years and above
- Singleton gestation
- Gestational age between 37 weeks 0 days to 41 weeks 3 days.

The exclusion criteria will include patients with conditions with high risk for PPH:

- Haemoglobin level <8g/dl
- Antepartum haemorrhage (Placenta Previa, Abruptio placentae)
- Multifetal pregnancy
- Previous history of PPH
- Polyhydramnios (AFI >25cm or DVP >8cm)
- Large uterine fibroid (at least one nodule with size >10cm) and/or any FIGO Type 0 fibroids
- Post-placental IUCD insertion
- Known coagulation disorders
- Known allergy to Misoprostol.

PART 3: Study Summary

Target population

Females 18 years and above

Date of Commencement (Expected or Actual)

11th January 2024 (Actual)

Status of Study

Actively recruiting

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The Investigational product and Auxiliary medical product; Misoprostol (Cytotec) and Oxytocin (Promptin) are registered products. The quality of the IPs has been assessed by the FDA. The applicant submitted the Summary of Product Characteristics (SmPC) and Package insert as part of the CTA.

Safety

The interventions to be compared in this trial have been used in previous trials (underlisted) with higher doses of misoprostol where no serious adverse events occurred. Although no serious adverse events are anticipated, excessive bleeding, infections, maternal risks and complications will be closely monitored in this trial.

- A meta-analysis of seventeen RCT studies by Conde-Agudelo et al, that evaluated the efficacy and safety of misoprostol in preventing PPH at caesarean section when administered through various routes, compared with either another uterotonic agent or placebo/no uterotonic agent.
- An RCT in Egypt by Abdelaleem et al, compared the efficacy of 400mcg intrauterine misoprostol to 10IU intravenous oxytocin infusion in reducing blood loss during and after caesarean section.
- A randomized controlled trial by Owonikoko et al determined the effect of sublingual misoprostol versus intravenous oxytocin in reducing blood loss at caesarean section, compared to blood loss at caesarean delivery using visual inspection and gravimetric method.

The following documents were reviewed and found satisfactory to fulfill the safety requirement of the trial:

PART 4: Scientific Discussion

1. Protocol sections on Adverse events reporting guidelines, End of Study definition, Risk to Benefit Ratio Assessment, Management and Accountability of Investigational Products (IP).
2. Independent Data and Safety Monitoring Board (DSMB) charter
3. Criteria for clinical trial termination
4. Medical Insurance for study participants

As a safety endpoint, the study stated that the intrauterine route of administration of 400mcg misoprostol will have a better side-effect profile when compared to 600mcg sublingual misoprostol in the prevention of postpartum haemorrhage,

Efficacy

Evaluation of the possible efficacy of the intervention was based on the information stated in the protocol. Potential benefits of the intervention stated in the protocol include:

- Efficacy in Preventing PPH
- Ease of Administration
- Reduced Morbidity and Mortality
- Low dose Intrauterine misoprostol which is affordable and has lower risk of SAEs

The literature review in the protocol provided summaries of various published studies highlighting the effectiveness of misoprostol in the reduction of intraoperative blood loss and blood loss after surgery.

As an efficacy endpoint, the study stated that the intrauterine route of administration of 400mcg misoprostol will be as effective as 600mcg sublingual misoprostol at preventing postpartum haemorrhage.

Overall comments

After initial review, the application was deferred with queries to be addressed by the applicant. Following the satisfactory response to all queries on the submission, the study was approved and issued a clinical trial certificate.

The applicant is committed to ensuring that the study is conducted in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

All participants will consent to the protocol prior to participation in any study-related activity.

PART 4: Scientific Discussion

Based on the assessment of medical and ethical principles, the anticipated benefits to the participant justify the foreseeable risks and inconveniences related to the conduct study.

PART 5: Application Review Process

The application was reviewed under the routine approval pathway with decision taken in 47 working days.

PART 6: Status after Review

Study was approved on 3rd January 2024. Applicant is required to submit monthly progress reports due to the short trial duration (3 months).

REFERENCES

1. Academic Clinical Trial Protocol revised version 2.0 signed and dated 15th September 2023.
2. Participant Information Leaflet version 2.0 dated September 2023
3. Study data collection tool (Proforma)
4. Data and Safety Monitoring Board (DSMB) Charter (KBTH DSMB, adopted from NIDDK NIH DSMB Charter 082213) version 2.0 dated September 2023
5. Pfizer Summary of Product Characteristics for Cytotec version 0.2, dated August 2017
6. FDA's Clinical Trial Assessment form version for Clinical Trial Application version 1.0 dated 2nd September 2019
7. Guidelines for Authorization of Clinical Trials of Medicines, Food Supplements, Vaccines and Medical Devices in Ghana
8. Guidelines for Good Clinical Practice in Ghana