Carbetocin for the prevention of postpartum hemorrhage

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KEY FINDINGS AND IMPLICATIONS FOR POLICY

Aligning to the Millennium Development Goal (MDG) of improving maternal health, the Department of Health (DOH) established the Safe Motherhood Program, while the Philippine Health Insurance Corporation (PhilHealth) implemented the Normal Spontaneous Delivery Package and the Maternity Care Package, both of which include coverage for normal deliveries for the first 4 births. Despite these programs and service coverage, maternal morbidity and mortality is still a concern in the Philippines, and the MDG for maternal health is still not met. Given such, there is a need to revisit the programs and packages and explore alternative interventions to reduce maternal morbidity and mortality.

Postpartum hemorrhage (PPH) is among the leading causes of maternal deaths in the Philippines, together with pre-eclampsia and eclampsia. To address PPH, active management of third stage of labor (AMTSL) is recommended by local and international clinical practice guidelines. In these CPGs, oxytocin is the standard drug of choice for the prevention of PPH.

This technology assessment focuses on carbetocin for prevention of PPH following elective cesarean section (CS). This assessment is limited to the indication approved by the Philippine Food and Drug Administration (FDA): for the prevention of uterine atony and PPH following elective CS under epidural or spinal anesthesia. Carbetocin has not been studied in cases involving emergency CS, classical CS, or anesthesia other than epidural or spinal. Also, limited studies had been conducted on women on vaginal delivery.

A panel consultation with key specialists revealed that obstetrician-gynecologists (OB-GYNs) seldom encounter uterine atony and PPH among elective CS patients. It was reported that carbetocin is used off-label, mostly for managing high-risk pregnancies, irrespective of the mode of delivery. These instances showed that the prevailing usage in local practice is not aligned with the FDA-approved indication of carbetocin. Furthermore, DOH program managers raised their concern regarding the possible abuse and misuse of carbetocin. Since carbetocin is considered as an abortifacient similar to misoprostol, there is a need to discuss its regulation with a wider range of stakeholders.

More evidence on the clinical effectiveness and safety of carbetocin is necessary to determine its optimal use in the public health sector. Due to potential ethical and safety issues, its market authorization also needs to be reviewed should it be reconsidered for listing in the Philippine National Formulary (PNF).

BACKGROUND

Definition and Burden of Disease

Maternal health remains a concern in the Philippines. In 2016, the number of registered maternal deaths reached a total of 1,483[1]. From 2012 to 2016, the reported maternal mortality ratio, that is, the number of reported maternal deaths per number of reported live births[2], ranges from 80.82 to 98.64 per 100,000 live births[1,3–10] (Table 1).

Table 1. Maternal mortality ratio in the Philippines, 2012 to 2016

Year	Number of maternal deaths	Number of live births	Maternal mortality ratio[a] (per 100,000 live births)
2016	1,483	1,731,289	85.66
2015	1,721	1,744,767	98.64
2014	1,570	1,748,857	89.77
2013	1,522	1,761,602	86.40
2012	1,447	1,790,367	80.82
2011	1,469	1,746,684	84.10
2010	1,719	1,782,981	96.41

Note: MMR manually computed from data on maternal deaths and live births.
(a) number of reported maternal deaths per number of live births.
MMR=maternal mortality ratio.
Source: Philippine Statistics Authority. Vital Statistics Report 2006 to 2010 [Internet]. 2015. Available from: https://psa.gov.ph/content/vital-statistics-report-2006-2010; Sinson FA, Rebanal LMR, Timbang TD. The 2014 Philippine Health Statistics [Internet]. 2014. Available from: http://www.doh.gov.ph/sites/default/files/publications/2014PHS_PDF.pdf.

Postpartum hemorrhage (PPH), defined as blood loss of 500 mL or more within 24 hours after birth that results in signs and symptoms of hemodynamic instability[11,12], is one of the leading causes of maternal deaths in the Philippines, together with pre-eclampsia and eclampsia[8] (Table **2**). In clinical terms, PPH is defined as blood loss of at least 500 mL in a vaginal delivery and at least 1000 mL in a cesarean section (CS) after birth that results in signs and symptoms of hemodynamic instability[11–13]. This assessment focuses on primary PPH, which occurs within 24 hours after infant delivery.

Table 2. Most common causes of maternal deaths in the Philippines, 2010 to 2014

Cause	ICD Code	Proportion from total maternal deaths				
		2010	2011	2012	2013	2014
PPH	O72	17%	17%	15%	14%	16%

Table 2. Most common causes of maternal deaths in the Philippines, 2010 to 2014

Cause	ICD Code	Proportion from total maternal deaths				
		2010	2011	2012	2013	2014
Pre-eclampsia	O14	12%	10%	14%	16%	14%
Eclampsia	O15	22%	20%	20%	20%	20%
Other	-	49%	53%	51%	50%	50%

"-" denotes not applicable.
ICD=International Classification of Diseases; PPH=postpartum hemorrhage.
Source: De Guzman JE, Dayrit MM, Salting PA, Dumbrique JI, Dee C, Dayrit MM, et al. Maternal Mortality Measurements Using National Surveys and Vital Statistics : Assessing the Quality and Content of Maternal Death Certificates. 2016.

The occurrence of PPH is in response to at least 1 of the following abnormalities: uterine atony, retained placental tissue or blood clots, genital tract lacerations or hematoma, and coagulopathy. Of the 4, uterine atony is the leading cause of PPH; it is observed in 70% of all cases of PPH[13]. Uterine atony is defined as the failure of the uterus to contract and retract after childbirth[12]. Risk for uterine atony is associated with overdistended uterus, uterine muscle fatigue, chorioamnionitis, uterine distortion or abnormality, and use of uterine-relaxing drugs[14]. Table 3 summarizes the clinical risk factors associated to uterine atony.

Table 3. Pathophysiology and risk factors of postpartum hemorrhage due to uterine atony

Pathophysiology	Risk factors
Overdistended uterus	multiple gestation
	polyhydramnios
	macrosomia
Uterine muscle fatigue	prolonged labor
	augmentation of labor
	prior PPH
Chorioamnionitis	prolonged ROM
Uterine distortion/abnormality	fibroids, placenta previa
Uterine-relaxing drug	beta mimetics, $MgSO_4$, anesthetic drugs

$MgSO_4$=magnesium sulfate; PPH=postpartum hemorrhage; ROM=rupture of membranes.
Source: Philippine Obstetrical and Gynecological Society. Clinical practice guidelines on Third Trimester Bleeding. Vol. 156. 2009.

Understanding Local Practice

Several existing clinical practice guidelines[11,13,15–22] (CPGs) promote the active management of third stage of labor (AMTSL) on all women during childbirth for the prevention of PPH.The third stage of labor happens from child delivery to placental delivery. Studies have found that AMTSL lowers maternal blood loss compared with expectant management, thus, reducing the risk for PPH. Recommendations from international guidelines include administration of uterotonics and cord clamping in AMTSL[11,13]; administration of uterotonics is the most important component of AMTSL[12].

In these CPGs, oxytocin is the standard drug of choice for the prevention and treatment of PPH. Carbetocin for the prevention of PPH is recommended by the Society of Obstetricians and Gynaecologists of Canada only for elective CS patients or those patients with at least 1 risk factor for PPH.

Locally, the Philippine Obstetrical and Gynecological Society (POGS) had developed a CPG on obstetric hemorrhage[12,14]; it also recommends AMTSL to attain adequate uterine tone and prevent PPH (Figure 1). Like in other CPGs, oxytocin is the standard drug for the prevention and treatment of PPH. Carbetocin is considered as one of the alternative treatments if adequate uterine tone is not reached after administration of oxytocin.

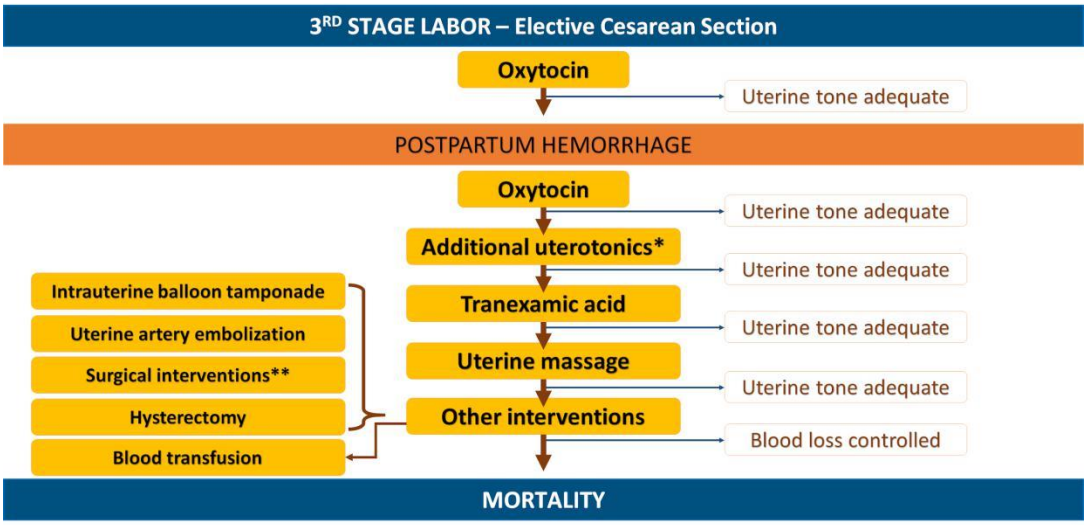

Figure 1. Algorithm for the prevention and treatment of postpartum hemorrhage based on the local clinical practice guidelines for obstetric hemorrhage
*additional uterotonics include carbetocin, carboprost, and methylergometrine.
**surgical interventions other than hysterectomy.
Source: Philippine Obstetrical and Gynecological Society. Clinical practice guideline on obstetric hemorrhage. 2014.

Despite these differences in the guidelines, there is a common pattern in the prevention of PPH: the practice of AMTSL with a highlight on the use of uterotonics and the use of oxytocin as the standard drug for the prevention of PPH. It is also important to note that the recommendation for carbetocin is limited and that its use is restricted.

Government Financing

There are currently 3 Philippine national government programs supporting maternal health: 1) the National Safe Motherhood Program, 2) the Normal Spontaneous Delivery Package, and 3) the Maternity Care Package.

Aligning to the Millennium Development Goal (MDG) of improving maternal health, the Department of Health (DOH) established the Safe Motherhood Program[23]; this program focuses on making pregnancy and childbirth safer by changing fundamental societal dynamics that influence decision making and by ensuring accessible quality emergency obstetrics and newborn care facilities. The program aims to establish a sustainable and cost-effective approach of delivering high-quality health services and to establish core knowledge base and support systems that facilitate the delivery of these services[23].

On the other hand, the Normal Spontaneous Delivery Package and Maternity Care Package of the Philippine Health Insurance Corporation (PhilHealth) include coverage for normal deliveries for the first 4 births[24]. These packages include fees from antepartum to postpartum care. PhilHealth also has case rates for obstetric conditions, such as hemorrhage following delivery of placenta.

Despite these programs and service coverage, maternal morbidity and mortality is still a concern in the Philippines and the MDG for maternal health is still not met. There might be a need to revisit the programs and packages and explore alternative interventions to reduce maternal morbidity and mortality.

UTEROTONIC AGENTS: CARBETOCIN AND OXYTOCIN

Indication

Oxytocin and carbetocin, a synthetic agonist of oxytocin, are agents that produce uterine contractions. They are classified as oxytocic agents. Oxytocin is indicated for the production of uterine contractions during the third stage of labor and to control postpartum bleeding or hemorrhage[25]. Carbetocin, on the other hand, is only indicated for the prevention of uterine atony and PPH following elective CS under epidural or spinal anesthesia[26,27]. It has not been studied in cases involving emergency CS, classical CS, or anesthesia other than epidural or spinal. Also, limited studies had been conducted on women on vaginal delivery. Currently, carbetocin is not available in the United States[26].

Mechanism of action

Carbetocin and oxytocin act similarly by binding to oxytocin receptors. Such action produces rhythmic uterine contractions, increases both the frequency and amplitude of existing contractions and the uterine tone, and enhances uterine involution early in postpartum. The only difference lies on the lower potency, longer duration of action, and rapid onset of action of carbetocin compared with oxytocin[25,26].

Adverse effects and drug interactions

Due to the similar mechanism of action of carbetocin and oxytocin, their adverse effects and drug interactions are also similar[25,26].

Dosage and route of administration

Carbetocin is administered intravenously as a single dose of 100 mcg/mL bolus slowly for 1 minute; oxytocin is administered through intravenous infusion or injected intramuscularly, for which the dose is

determined by the uterine response of the patient[25,26].

Contraindication

Carbetocin and oxytocin have similar contraindications, which include hypersensitivity to the drug, pregnancy, vascular diseases, water intoxication, and others. Due to the longer duration of carbetocin, it is contraindicated to be administered prior to the delivery of the infant. Administration to patients with eclampsia and pre-eclampsia should be considered with precaution; similarly, administration of additional doses carbetocin should be done with precaution[25,26].

CONTEXT AND POLICY ISSUES

Last January 2017, the DOH Pharmaceutical Division (PD) received applications for the inclusion of carbetocin to the Philippine National Formulary (PNF) from Quirino Memorial Medical Center, Philippine General Hospital, and Valenzuela Medical Center. Furthermore, 10 hospitals had been granted exemption on the use of carbetocin from 2014 to 2017, namely Southern Philippines Medical Center, Dr. Jose Fabella Memorial Hospital, East Avenue Medical Center, Vicente Sotto Memorial Medical Center, Valenzuela Medical Center, Rizal Medical Center, Quirino Memorial Medical Center, Philippine General Hospital, Jose R. Reyes Memorial Medical Center, and Armed Forces of the Philippines Medical Center.

The rationale provided by the proponents for these requests for inclusion and exemption is the claim that carbetocin can potentially reduce maternal morbidity and mortality due to PPH because of its potentially better efficacy and safety compared with the drugs currently listed in the PNF (i.e., oxytocin). In light of these policy concerns, the health technology assessment of carbetocin has commenced.

In the Philippine setting, oxytocin is the drug of choice for AMTSL. Carbetocin, on the other hand, can only be used on a specific indication as previously stated. The potential advantage of carbetocin, according to the applications for inclusion, includes its rapid onset of action and long acting duration, which, in turn, minimizes medication errors in infusions and reduces staff hours by reducing the time needed to sustain and monitor the maintenance of adequate uterine tone.

The oxytocin 10 IU/mL, 1 mL ampule has a reference price of PHP 76.92 based on the 2017 Philippine Drug Price Reference Index[28]. The current price offer for carbetocin 100 mcg, 1 mL ampule is **PHP 933.00** (Table 4).

Table 4. Price comparison of carbetocin and oxytocin in the Philippines

Uterotonic	Price (PHP)
Carbetocin	933.00[a]
Oxytocin	76.92[b]

(a) Based on the 2017 DPRI.
(b) Based on the price offer from the manufacturer. DPRI=Drug Price Reference Index.
Source: Department of Health - Philippines. 2017 DPRI Fifth Edition. 2017;0–22.

As the price of carbetocin is significantly higher than oxytocin, evidence on its superiority (i.e., either in efficacy or safety), within the bounds of its indication, must be established to justify its inclusion in the PNF.

REVIEW OF CLINICAL EFFICACY & EFFECTIVENESS

Pre-consultation literature review and panel consultation

A panel consultation was held to engage and consult various key stakeholders on the current local standards of care and available treatment alternatives. The panel was composed of obstetrician-gynecologists (OB-GYNs) from POGS, DOH program managers, and members from the benefit package development teams of PhilHealth. The objectives of the panel consultation were 1) to inform key stakeholders on the process of HTA, 2) to have a better understanding on the local standard of care using the treatment pathway of the locally recognized CPG, and 3) to establish and finalize the scope and both the research and policy questions for the HTA.

Prior to the panel consultation, an initial literature review of randomized clinical trials (RCTs), systematic reviews, meta-analyses, and cost-effectiveness analyses of carbetocin was done. This literature review was focused on studies comparing carbetocin as an alternative to oxytocin for the prevention of PPH in elective CS patients. Evidence on the burden of disease and information on standard practices were also searched and reviewed.

The summary of findings of the pre-consultation literature review is as follows:

1) the clinical efficacy and safety profile of carbetocin and oxytocin are comparable
2) there is no difference in the incidence of PPH between carbetocin and oxytocin
3) there is a reduced need for additional uterotonics and uterine massage in patients who are given carbetocin versus oxytocin

Based on the review of the local CPG on obstetric hemorrhage, the schematic diagram of the assumed patient journey for the assessment is shown in Figure 2[12].

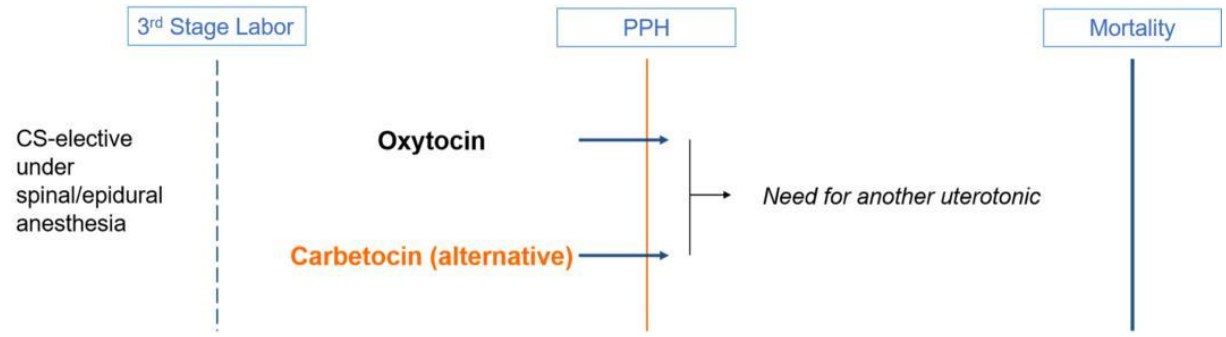

Figure 2. Schematic diagram of the assumed patient journey
CS=cesarean section; PPH=postpartum hemorrhage.
Source: Philippine Obstetrical and Gynecological Society. Clinical practice guideline on obstetric hemorrhage. 2014.

During the panel consultation, the panel was informed of the HTA process; the importance of adhering to the FDA-approved product information and the lack of clinical studies on other usage of carbetocin were emphasized. In refining the research question for the HTA of carbetocin, it was agreed that the target population will be elective CS patients who are at high risk for PPH. This population was selected to reflect the reality in government hospitals, which receive referrals for managing high-risk pregnancies. During the panel consultation, the most commonly observed conditions that predispose a person to be at high risk for PPH were identified in

the following order: 1) placenta previa, 2) multiple gestation, 3) fetal macrosomia, and 4) previous event for PPH.

According to the OB-GYNs, oxytocin is very inadequate in handling these high-risk pregnancies given the day to day government hospital activities; the OB-GYNs had also stated that they seldom encounter uterine atony and PPH among elective CS patients. Although the PNF exemption limits the use of carbetocin as prevention for PPH in elective CS patients, they stated that carbetocin was often used in managing PPH regardless of the mode of delivery; they also mentioned that carbetocin usage was noted in the medical records.

These instances showed that prevailing usage in local practice is not aligned with the FDA-approved indication of carbetocin. Although the presence of unmet need is present in managing pregnancies that are at high risk for PPH, concerns were raised by the DOH program managers regarding the possible abuse and misuse of carbetocin. The program managers mentioned that listing of carbetocin in the PNF would translate to the availability of the drug in all government facilities, which may give way to the use carbetocin for other indications. Furthermore, carbetocin is considered as a potential abortifacient similar to misoprostol, which leads to a bigger policy issue.

While the pre-consultation literature review included the CPG on obstetric hemorrhage published in 2014, POGS mentioned that an updated CPG was published in 2016. To reflect the ideal clinical pathway on the local practice, the algorithm was redeveloped (Figure 3). The primary outcome to be measured for efficacy is the event of PPH. Additional outcome to be measured is the use of additional uterotonics. While the pathway may vary depending on the risk factors, the pathway is most commonly being followed in the treatment of elective CS patients who are high risk for PPH.

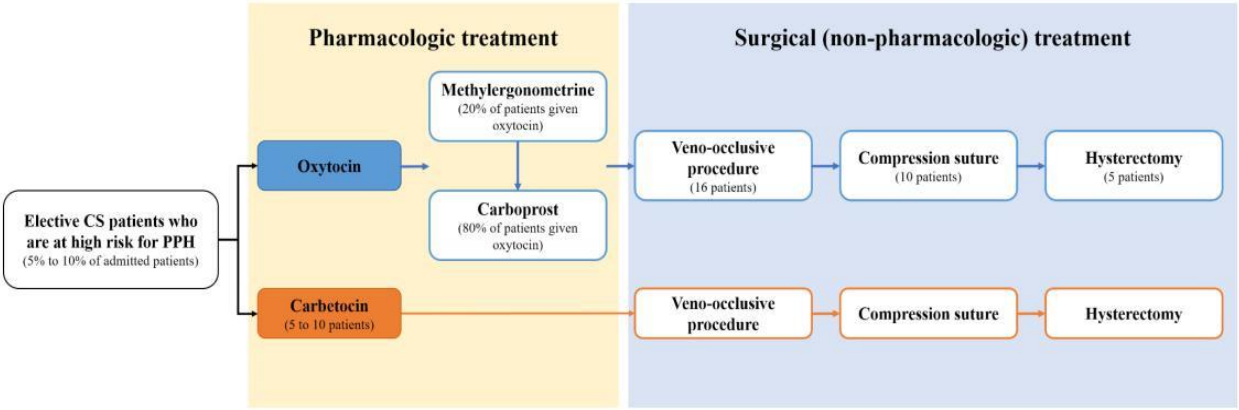

Figure 3. Agreed treatment pathway with approximated frequencies and proportions of patients
Note: This treatment pathway resulted from the discussions during the panel consultation. The values provided are only approximates and are still subject to validation.

For the conduct of the economical evaluation, the panel agreed that the health system perspective shall be used, which does not include productivity costs of the patient. Other important clinical outcomes to be included, based on the panel consultation, were length of hospital stay, number of admissions to the intensive care unit, manpower, use of antibiotics, amount of blood loss, blood pressure, and cardiac rate. Non-pharmacological costs to be considered were surgical costs, which includes the costs for an anesthesiologist, sutures, and other additional manpower. Costs for blood transfusion were to be included, too. Other pharmacological costs to be included were costs for syringes, cotton, and intravenous cannula and tubing.

Systematic review

To assess and compare the clinical efficacy and safety of carbetocin versus oxytocin, a systematic review of eligible randomized clinical trials was planned and conceptualized. The preliminary search strategy for the systematic review is presented in this section. Since there were no specific studies submitted by the applicant for the population and topic of interest, evidence was planned to be mainly gathered from published findings of randomized controlled trials.

The objective of this review was to assess the efficacy and safety of carbetocin in the prevention of uterine atony and PPH compared with oxytocin among elective CS patients under epidural or spinal anesthesia at high risk for PPH. Specifically, the objectives were 1) to compare the incidence of PPH among patients given carbetocin versus those given oxytocin, and 2) to compare the efficacy of carbetocin versus oxytocin in terms of the secondary outcomes, which are a) maternal death, b) severe morbidity, c) need for blood transfusion, d) use of additional therapeutic uterotonics, e) additional surgical treatment for PPH (Figure 3) adverse events.

Search strategy

Journal articles were to be gathered from *electronic databases* (CINAHL, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Pregnancy and Childbirth Groups Trials Register, Database of Abstracts of Reviews of Effects [DARE], EBSCOhost, EMBASE, Herdin, LILACS, PUBMED/MEDLINE, Science direct, Scopus, and Web of Science) and *clinical trial registries* (ClinicalTrials.gov, European Union Clinical Trials Registry, International Clinical Trials Registry Platform [ICTRP], and Current Controlled Trials). Additionally, *grey literature* was to be gathered and reviewed from OpenGrey, GreyNet, Grey Literature Report, and BIOSIS Previews. The search was designed to be limited to articles that were published up to 10 years ago.

Selection criteria

The planned selection criteria are based on the 1) study design, 2) population, intervention, comparator and outcome (PICO), and 3) language. Table 5 summarizes the description of each aforementioned criteria.

Table 5. Planned selection criteria

Criterion	Description
Study design	All randomized clinical trials
PICO	***Population***: Elective CS patients at high risk for PPH ● PPH is defined as blood loss of at least 1000 mL within 24 hours from birth. ● High risk for PPH is defined by, but not limited to, having the following conditions: (1) placenta previa (2) multiple gestation (3) fetal macrosomia (4) previous event of PPH. ● Patients who are contraindicated for carbetocin are excluded ***Intervention:*** Carbetocin 100 mcg/mL ***Comparator***: Oxytocin ***Outcomes***: Incidence or events of PPH (primary outcome); maternal death, severe morbidity, need for blood transfusion, use of additional therapeutic

Table 5. Planned selection criteria

Criterion	Description
	uterotonics, additional surgical treatment for PPH (Figure 3), and adverse events (secondary outcomes)
Language	English

CS=cesarean section; PICO=population, intervention, comparator, and outcome; PPH=postpartum hemorrhage.

Initial literature search was to be conducted within the identified databases using the following keywords and MeSH terms: “postpartum hemorrhage”, “postpartum haemorrhage”, “carbetocin”, and “elective cesarean”. Based on the abstracts of the resulting studies, data on the author, year of publication, title, study design, patient characteristics, and treatment arms were to be collected. If the study would satisfy the desired study design, patient characteristics, and treatment arms (Table 5), it would be included for full-text review.

Critical Appraisal of Included Studies

Subsequently, the following data were to be further extracted from the studies that will be initially included in the first round of literature search: study length, country, sample size, number of participants in the experimental and control groups, continuation rate and discontinuation rationale, risk factors, primary and secondary outcome measures, quality of life, conclusion, and sponsorship. If the study would satisfy the rest of the specified criteria in Table 5, said study would be included for final review. Finally, a PRISMA diagram was planned to be utilized to show the process of study selection – from database searching and removal of duplicates, initial screening, and final inclusion. The risk of bias assessment was to be done according to the Cochrane Handbook. Publication bias was to be qualitatively and quantitatively evaluated using Deek’s Funnel Plot and Egger’s Test, respectively.

Initial search results

Initial literature search was conducted using the free electronic databases (i.e., PUBMED/MEDLINE and Google Scholar) from March 15 to 30, 2018 using the keywords “postpartum hemorrhage”, “postpartum haemorrhage”, “carbetocin”, and “elective cesarean”. The number of search results per database as well as the combination of the aforementioned keywords using Boolean operators is summarized in Table 6.

Table 6. Initial search results per database and combination of keywords

Keywords	PUBMED/MEDLINE	Google Scholar
“Carbetocin" AND "Postpartum Hemorrhage"	65	661
“Carbetocin" AND "Postpartum Haemorrhage"	25	581

Table 6. Initial search results per database and combination of keywords

Keywords	PUBMED/MEDLINE	Google Scholar
“Carbetocin" AND "Postpartum Hemorrhage" AND Elective Cesarean	12	171
“Carbetocin" AND "Postpartum Haemorrhage" AND Elective Cesarean	4	165

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