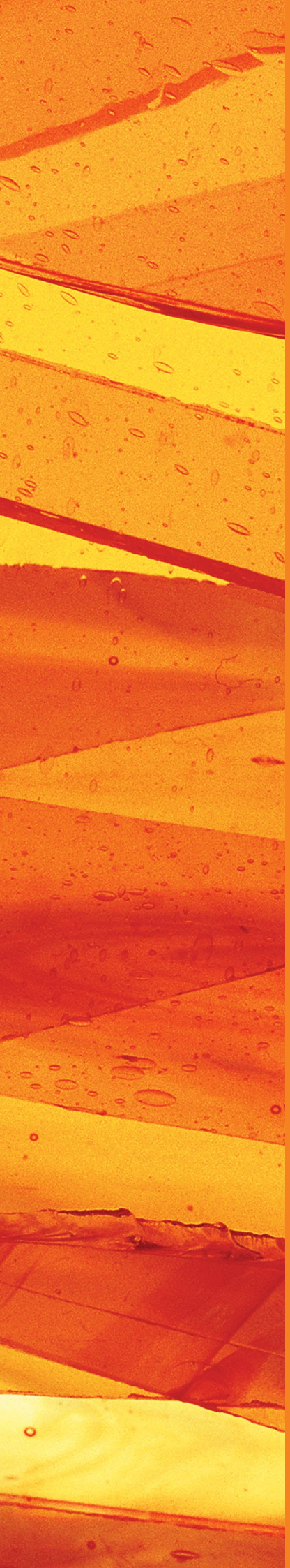


WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

World Health Organization

WHO recommendations

Uterotonics for the prevention of postpartum haemorrhage

World Health Organization

WHO recommendations: uterotonics for the prevention of postpartum haemorrhage

ISBN 978-92-4-155042-0

Contents

Acknowledgements

The World Health Organization (WHO) gratefully acknowledges the contributions of many individuals and organizations to the updating of these recommendations. Work on this update was initiated and coordinated by Olufemi Oladapo and Joshua Vogel of the WHO Department of Reproductive Health and Research. Fernando Althabe, Olufemi Oladapo, Özge Tunçalp and Joshua Vogel of the WHO Department of Reproductive Health and Research and Maurice Bucagu and Nathalie Roos of the WHO Department of Maternal, Newborn, Child and Adolescent Health, were members of the WHO Steering Group, which managed the guideline updating process. Nino Berdzuli, Paata Chikvaidze, Bremen De Mucio, Hayfa Elamin, Fatu Forna, Nilmini Hemachandra, Chandani Anoma Jayathilaka, Ramez Khairi Mahaini, Lamia Mahmoud, Léopold Ouedraogo, Howard Sobel, Claudio Sosa, Meera Thapa Upadhyay and Souleymane Zan were WHO regional and country office staff members who contributed to the technical consultations.

WHO extends its sincere thanks to Oluwarotimi Ireti Akinola, Shubha Allard, Melania Maria Ramos de Amorim, Brendan Carvalho, Catherine Deneux-Tharaux, Sue Fawcus, Caroline Homer, Simon Lewin, Tippawan Liabsuetrakul, Anita Maepioh, Martin Meremikwu, Suellen Miller, Rintaro Mori, Hiromi Obara, Rachel Plachcinski, Hayfaa Wahabi and Dilys Walker who served as members of the Guideline Development Group (GDG), and to Ashraf Nabhan for chairing the technical consultations. We also thank Michel Boulvain, Jemima A. Dennis-Antwi, Vanora Hundley, Tamar Kabakian-Khasholian, Barbara Levy, Lawal O. Oyeneyin, Alison Wright and Qian Xu who were members of the External Review Group (ERG).

We appreciate the contributions of the members of the Executive Guideline Steering Group (GSG) during the scoping and prioritization exercise that took place as part of the guideline updating process. Special thanks are due to the authors of the Cochrane systematic reviews used in this update for their assistance and collaboration in updating them.

Edgardo Abalos, Mónica Chamillard, Virginia Diaz, Soo Downe, Kenneth Finlayson, Ioannis Gallos, Leanne Jones, Frances Kellie, Theresa Lawrie, Argyro Papadopoulou, Julia Pasquale and Myfanwy Williams were members of the Evidence Synthesis Group (ESG), who performed quality appraisal of the scientific evidence, and drafted the corresponding narrative evidence summaries and Evidence to Decision frameworks. Soo Downe, Kenneth Finlayson, Ioannis Gallos and Theresa Lawrie led the teams that conducted systematic reviews to inform the guideline. Joshua Vogel and Olufemi Oladapo double-checked the corresponding Summary of Findings tables and revised the narrative summaries and Evidence to Decision frameworks. Joshua Vogel and Olufemi Oladapo drafted the final guideline document before it was reviewed by other members of the WHO Steering Group and the GDG. The ERG peer reviewed the final document prior to clearance by WHO for publication.

We acknowledge the following observers at the technical consultations, who represented various organizations: Deborah Armbruster and Mary-Ellen Stanton (United States Agency for International Development [USAID]), Jeffrey Smith (Jhpiego), Jerker Liljestrand (Bill & Melinda Gates Foundation), Sally Tracy (International Confederation of Midwives [ICM]), Gerard Visser (International Federation of Gynaecology and Obstetrics [FIGO]) and Beverly Winikoff (Gynuity Health Projects).

This work was funded by USAID and the UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), a cosponsored programme executed by WHO. The views of the funding bodies have not influenced the content of these recommendations.

Editing: Green Ink, United Kingdom

Layout: minimum graphics, New Zealand

Acronyms and abbreviations

CERQual	Confidence in the Evidence from Reviews of Qualitative research
CREP	Centro Rosarino de Estudios Perinatales
DOI	declaration of interest
ERG	Evidence Review Group
ESG	Evidence Synthesis Group
EtD	Evidence to Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSG	Guideline Steering Group
HRP	The UNDP–UNFPA–UNICEF–WHO–World Bank Special Programme of Research, Development and Research Training in Human Reproduction
ICM	International Confederation of Midwives
ICN	International Council of Nurses
IM	intramuscular
IPA	International Pediatric Association
IU	international units
IV	intravenous
µg	microgram
MNH	maternal and newborn health
PO	per os (orally)
PICO	population (P), intervention (I), comparator (C), outcome (O)
PPH	postpartum haemorrhage
SoF	Summary of Findings
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Executive summary

Introduction

Postpartum haemorrhage (PPH) is commonly defined as a blood loss of 500 ml or more within 24 hours after birth, and affects about 5% of all women giving birth around the world. Globally, nearly one quarter of all maternal deaths are associated with PPH, and in most low-income countries it is the main cause of maternal mortality. Improving care during childbirth to prevent PPH is a necessary step towards the achievement of the health targets of the third Sustainable Development Goal (SDG 3), particularly target 3.1: reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030. Efforts to prevent and reduce morbidity and mortality due to PPH can help address the profound inequities in maternal and perinatal health globally. To achieve this, skilled health personnel, health managers, policy-makers and other stakeholders need up-to-date and evidence-informed recommendations to guide clinical policies and practices.

In 2017, an Executive Guideline Steering Group (GSG) for World Health Organization (WHO) maternal and perinatal health recommendations prioritized the updating of the existing WHO recommendations on the use of uterotonics for PPH prevention, in response to the availability of new evidence. The recommendations in this document thus supersede previous WHO recommendations on the use of uterotonics for PPH prevention as published in the 2012 guideline, *WHO recommendations for the prevention and treatment of postpartum haemorrhage*.

Target audience

The primary audience for these recommendations includes health professionals who are responsible for developing national and local health care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women and their newborns during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

Guideline development methods

The updating of these recommendations was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were initially developed and updated using the following process:

i. identification of priority questions and outcomes;

ii. retrieval of evidence;

iii. assessment and synthesis of evidence;

iv. formulation of the recommendations; and

v. planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

Updated systematic reviews were used to prepare evidence profiles for the priority questions. The quality of the scientific evidence underpinning the recommendations was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for quantitative evidence and the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach for qualitative evidence. The GRADE Evidence to Decision (EtD) framework – an EtD tool that encompasses intervention effects, values, resource use, equity, acceptability and feasibility criteria – was used to guide the formulation of recommendations by the Guideline Development Group (GDG) – an international group of experts convened for the purpose of updating these recommendations – at two GDG meetings in September and October 2018.

Recommendations

The two GDG meetings led to four main recommendations and six sub-recommendations on the use of uterotonics for PPH prevention. Based on assessments of the GRADE EtD criteria, which informed the direction, and in some instances the specific context of the recommendation, the GDG classified recommendations using the four categories defined below.

Recommended: This category indicates that the intervention or option should be implemented.

Not recommended: This category indicates that the intervention or option should not be implemented.

Recommended only in specific contexts ("context-specific recommendation"): This category indicates that the intervention or option is applicable only to the condition, setting or population specified in the recommendation, and should only be implemented in these contexts.

Recommended only in the context of rigorous research ("research-context recommendation"): This category indicates that there are important uncertainties about the intervention or option. In such instances, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

To ensure that each recommendation is correctly understood and applied in practice, the contributing experts provided additional remarks where needed. Where the GDG made a context-specific recommendation, further detail was included about the particular context and which key issues needed to be examined. Users of the guideline should refer to these remarks, which are presented directly beneath each recommendation (section 3.2). The recommendations on uterotonics for PPH prevention are summarized in Table 1.

Derivative products from these recommendations will include policy briefs for programme managers to enable application of the recommendations at different levels of care. In accordance with the process for updating WHO maternal and perinatal health recommendations, a systematic and continuous process of identifying and bridging evidence gaps following implementation of these recommendations will be employed. In the event that new evidence that could potentially impact the current evidence base is identified, the recommendations will be updated. WHO welcomes suggestions regarding additional questions for inclusion in future updates of these recommendations.

Table 1. WHO recommendations on the use of uterotonics for the prevention of postpartum haemorrhage (PPH)

Context	Recommendation	Category of recommendation
Efficacy and safety of uterotonics for PPH prevention	**1.** The use of an effective uterotonic for the prevention of PPH during the third stage of labour is recommended for all births. To effectively prevent PPH, only ***one*** of the following uterotonics should be used: • oxytocin (Recommendation 1.1) • carbetocin (Recommendation 1.2) • misoprostol (Recommendation 1.3) • ergometrine/methylergometrine (Recommendation 1.4) • oxytocin and ergometrine fixed-dose combination (Recommendation 1.5).	Recommended
	1.1 The use of oxytocin (10 IU, IM/IV) is recommended for the prevention of PPH for all births.	Recommended
	1.2 The use of carbetocin (100 μg, IM/IV) is recommended for the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics.	Context-specific recommendation
	1.3 The use of misoprostol (either 400 μg or 600 μg, PO) is recommended for the prevention of PPH for all births.	Recommended
	1.4 The use of ergometrine/methylergometrine (200 μg, IM/IV) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use.	Context-specific recommendation
	1.5 The use of a fixed-dose combination of oxytocin and ergometrine (5 IU/500 μg, IM) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use.	Context-specific recommendation
	1.6 Injectable prostaglandins (carboprost or sulprostone) are not recommended for the prevention of PPH.	Not recommended
Choice of uterotonics for PPH prevention	**2.** In settings where multiple uterotonic options are available, oxytocin (10 IU, IM/IV) is the recommended uterotonic agent for the prevention of PPH for all births.	Recommended
	3. In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics (carbetocin, or if appropriate ergometrine/methylergometrine, or oxytocin and ergometrine fixed-dose combination) or oral misoprostol is recommended for the prevention of PPH.	Recommended
	4. In settings where skilled health personnel are not present to administer injectable uterotonics, the administration of misoprostol (400 μg or 600 μg, PO) by community health workers and lay health workers is recommended for the prevention of PPH.	Recommended

IM: intramuscular; IU: international units; IV: intravenous; PO: orally

1. Introduction

1.1 Background

An estimated 303 000 women and adolescent girls died as a result of pregnancy and childbirth-related complications in 2015, and around 99% of these deaths occurred in low-resource settings *(1)*. Obstetric haemorrhage, especially postpartum haemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide *(1)*. In most low-income countries, PPH is the leading cause of maternal deaths. Thus, improving access to safe and effective interventions to prevent PPH is critical to World Health Organization (WHO) strategic priorities (particularly universal health coverage) for achieving the targets of the third Sustainable Development Goal (SDG 3) *(2,3)*.

International human rights law includes fundamental commitments of States to enable women and adolescent girls to survive pregnancy and childbirth, as part of their enjoyment of sexual and reproductive health and rights, and living a life of dignity *(4)*. WHO envisions a world where "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" *(5)*. To provide good-quality care, skilled health personnel at all levels of the health system need to have access to appropriate medications and training in relevant procedures *(6)*. Health care providers, health managers, health policy-makers and other stakeholders also need up-to-date, evidence-informed recommendations to guide clinical policies and practices, in order to optimize quality of care and improve health care outcomes.

PPH is commonly defined as a blood loss of 500 ml or more within 24 hours after birth, and affects about 5% of all women giving birth around the world *(7,8)*. Severe maternal complications, such as organ dysfunction or death, generally occur following substantial blood loss that compromises maternal haemodynamic stability. Uterine atony is the most common cause of PPH and a leading cause of PPH-related maternal mortality worldwide *(1)*. Genital tract trauma (including vaginal or cervical lacerations and uterine rupture), retained placental tissue or maternal bleeding disorders can cause PPH. Although the majority of women presenting with PPH have no identifiable risk factor, grand multiparity, prolonged labour, prior history of PPH and multiple gestation are obstetric conditions that are associated with an increased risk of bleeding after birth *(9)*. In addition, anaemia is a common aggravating factor *(10)*. The majority of PPH-associated complications could be avoided by the use of prophylactic uterotonics during the third stage of labour (i.e. the time between the birth of the baby and complete expulsion of the placenta.

WHO has established a new process for prioritizing and updating maternal and perinatal health (MPH) recommendations, whereby an international group of independent experts – the Executive Guideline Steering Group (GSG) – oversees a systematic prioritization of MPH recommendations in most urgent need of updating *(11)*. Recommendations are prioritized for updating on the basis of changes or important new uncertainties in the underlying evidence base on benefits, harms, values placed on outcomes, acceptability, feasibility, equity, resource use, cost-effectiveness or factors affecting implementation. The Executive GSG prioritized the updating of the existing WHO recommendations on uterotonics for the prevention of PPH in anticipation of the publication of new and potentially important evidence on these interventions.

These updated recommendations were developed in accordance with the standards and procedures in the *WHO guideline development handbook*, including synthesis of available research evidence, use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[1] and GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual)[2] methodologies, and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and

[1] Further information is available at: http://www.gradeworkinggroup.org/

[2] Further information is available at: https://www.cerqual.org/

stakeholders *(12)*. The recommendations published in this document thus supersede the previous recommendations on the use of uterotonics for PPH prevention that were published in 2012 in the *WHO recommendations for the prevention and treatment of postpartum haemorrhage (13)*.

1.2 Aim

The primary aim of these recommendations is to improve the quality of care and outcomes for women giving birth, as they relate to PPH and its complications. These recommendations thus provide a foundation for sustainable implementation of routine uterotonic use in the immediate postpartum period globally.

1.3 Target audience

The primary audience includes health professionals who are responsible for developing national and local health care guidelines and protocols (particularly those related to PPH prevention and treatment) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners and obstetricians, as well as managers of maternal and child health programmes, and relevant staff in ministries of health and training institutions, in all settings.

These recommendations will also be of interest to women giving birth in a range of resource settings (low to high), as well as members of professional societies involved in the care of pregnant women, staff of nongovernmental organizations concerned with promoting people-centred maternal care, and implementers of maternal and perinatal health programmes.

1.4 Scope of the recommendations

The scope of these recommendations relates to the use of uterotonics during the third stage of labour for the prevention of PPH. The population of interest are women in the third stage of labour, regardless of mode of birth (vaginal birth or caesarean section) or birth setting (hospital or community setting[1]). Persons affected by these recommendations include all pregnant women in low-, middle- and high-income settings.

In 2012, WHO made recommendations on four uterotonic options: oxytocin; misoprostol; ergometrine/methylergometrine; and the fixed-dose combination of oxytocin and ergometrine. This update has considered not only those four options but also three additional options: carbetocin; injectable prostaglandins; and misoprostol plus oxytocin combination. For this update, evidence on efficacy has been informed primarily by a large Cochrane systematic review with a network meta-analysis of all seven uterotonic options, rather than individual systematic reviews, which were used for the recommendations published in 2012.

In formulating these recommendations, the GDG reviewed the evidence for all uterotonic options that have been investigated for PPH prevention, whether the studies compared uterotonics with placebo/no uterotonic, or compared them with other uterotonic options. These studies included use of single uterotonic agents (oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, injectable prostaglandins) and combinations of uterotonic agents (oxytocin plus ergometrine, and misoprostol plus oxytocin). Brief descriptions of the pharmacological characteristics, storage and transport requirements of these uterotonic options are presented in Table 2.

[1] "Community" was considered to include primary health care settings or in the home. However, self-administration of a uterotonic by women was not included.

Table 2. Characteristics of uterotonics options evaluated for the prevention of postpartum haemorrhage (PPH)

Characteristics	Oxytocin	Carbetocin	Misoprostol	Injectable prostaglandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Brief description *(14,15)*	Synthetic cyclic peptide form of the naturally occurring posterior pituitary hormone Binds to oxytocin receptors in the uterine myometrium, stimulating contraction of this uterine smooth muscle by increasing the sodium permeability of uterine myofibrils	Long-acting synthetic analogue of oxytocin with agonist properties Binds to oxytocin receptors in the uterine smooth muscle, resulting in rhythmic contractions, increased frequency of existing contractions, and increased uterine tone	Synthetic analogue of natural prostaglandin E1 Has oxytocic properties, inhibits gastric acid and pepsin secretion, and enhances gastric mucosal resistance to injury	Injectable prostaglandins (systemic) trialled for PPH prevention include prostaglandin F2α analogues (carboprost), prostaglandin E2 (dinoprostone) and prostaglandin E2 analogues (sulprostone)	Ergometrine and methylergometrine are ergot alkaloids that increase uterine muscle tone by causing sustained uterine contractions	Fixed-drug combination[a] – oxytocin (5 IU) plus ergometrine (500 μg)	See misoprostol and oxytocin Combination agents not in synthetic (fixed-dose) or naturally occurring forms
Pharmaco-kinetics *(14,15)*	Intravenous (IV): almost immediate action with peak concentration after 30 minutes Intramuscular (IM): slower onset of action, taking 3–7 minutes, but produces a longer-lasting clinical effect of up to 1 hour Half-life: 1–6 minutes	IV: sustained uterine contractions within 2 minutes, lasting for about 6 minutes and followed by rhythmic contractions for 60 minutes IM: sustained uterine contractions lasting for about 11 minutes and rhythmic contractions for 120 minutes Half-life: 40 minutes	Absorbed 9–15 minutes after sublingual, oral, vaginal or rectal use Oral and sublingual routes have the advantage of rapid onset of action, while the vaginal and rectal routes result in prolonged activity and greater bioavailability Half-life: 20–40 minutes	IM: 15–60 minutes to peak plasma concentration Half-life: 8 minutes	IM: onset of action within 2–3 minutes, lasting for about 3 hours IV: onset of action within 1 minute, lasting 45 minutes (although rhythmic contractions may persist for up to 3 hours) Half-life: 30–120 minutes	See oxytocin and ergometrine IM: latent period for the uterine response is about 2.5 minutes; uterotonic effects last for around 3 hours *(16)* Half-life: 1–6 minutes (oxytocin) and 30–120 minutes (ergometrine)	See misoprostol and oxytocin

Characteristics	Oxytocin	Carbetocin	Misoprostol	Injectable prostaglandins	Ergometrine	Oxytocin plus ergometrine	Misoprostol plus oxytocin
Storage and transport *(17)*	Requires protection from light, and storage at 2–8 °C[b] to prolong shelf life	A heat-stable formulation of carbetocin[c] is available	Does not have any special storage requirements. Tablets should be kept in tightly closed containers and protected from humidity.	Requires storage at 2–8 °C[b] to prolong shelf life	Requires protection from light, and storage at 2–8 °C[b] to prolong shelf life	See oxytocin and ergometrine.	See misoprostol and oxytocin
WHO Model List of Essential Medicines *(18)*	Listed: 10 IU in 1 ml ampoule for injection	Not listed	Listed: 200 μg tablets[d] and 25 μg tablets	Not listed.	Listed: Ergometrine (hydrogen maleate) 200 μg in 1 ml ampoule for injection	Oxytocin and ergometrine are listed separately The fixed-dose combination of oxytocin plus ergometrine (5 IU/500 μg) is not listed	See misoprostol and oxytocin

IM: intramuscular; IU: international units; IV: intravenous; PO: orally

[a] Syntometrine® (500 μg ergometrine maleate/5 IU oxytocin)

[b] Due consideration should be given to the manufacturer's instructions on storage and transport.

[c] The heat-stable formulation of carbetocin differs from the existing non-heat-stable formulation of carbetocin only in its excipients. An excipient is an inactive substance that serves as the vehicle or medium for the active ingredients.

[d] For the prevention and treatment of PPH where oxytocin is not available or cannot be safely used, and for the management of incomplete abortion and miscarriage.

The priority questions (and sub-questions) that guided evidence synthesis and decision-making for these recommendations are presented in Table 3 using the population (P), intervention (I), comparator (C), outcome (O) (PICO) format.

Table 3. Priority questions for development of the recommendations

1	For women in the third stage of labour (P), does the use of oxytocin for prevention of PPH (I), compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
2	For women in the third stage of labour (P), does the use of carbetocin for prevention of PPH (I), compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
3	For women in the third stage of labour (P), does the use of misoprostol for prevention of PPH (I), compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
4	For women in the third stage of labour (P), does the use of ergometrine/methylergometrine for prevention of PPH (I), compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
5	In women in the third stage of labour (P), does the use of oxytocin plus ergometrine for prevention of PPH (I) compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
6	For women in the third stage of labour (P), does the use of injectable prostaglandins for prevention of PPH (I), compared with placebo or no treatment (C), improve maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen should be used?
7	For women in the third stage of labour (P), is the use of any uterotonic agent(s) (oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, injectable prostaglandins, oxytocin plus ergometrine, misoprostol plus oxytocin) for prevention of PPH (I) compared with other uterotonic agents (oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, injectable prostaglandins, oxytocin plus ergometrine, misoprostol plus oxytocin) (C), safer and more effective for improving maternal and perinatal outcomes? ■ If so, what route of administration and dosing regimen of such uterotonic agent(s) should be used?

The GDG initially considered the comparisons of each uterotonic option (single agent or combination regimen) with placebo/no uterotonic to assess the efficacy and safety of each uterotonic option separately (PICO questions 1–6). This approach was taken to determine if each uterotonic can be individually applied for PPH prophylaxis in situations where other uterotonic agents are not available. Then, the GDG reviewed the comparative efficacy and safety of each uterotonic option (single agent or combination regimen) with each of the other uterotonic options to determine the most efficacious uterotonic agent with the best side-effect profile – the uterotonic of choice (PICO question 7).

2. Methods

The updated recommendations were developed using the standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (12)*. In summary, the process included: (i) identification of the priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of the recommendations; and (v) planning for the dissemination, implementation, impact evaluation and future updating of the recommendations.

Six main groups participated in this process, with their specific roles described in the following sections.

2.1 Executive Guideline Steering Group (2017–2019)

The Executive Guideline Steering Group (GSG) is an independent panel of 14 external experts and relevant stakeholders from the six WHO regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and Western Pacific Region. The Executive GSG advises WHO on the prioritization of new and existing PICO questions in maternal and perinatal health for development or updating of recommendations *(11)*.

2.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health managed the process of updating the recommendations. The WHO Steering Group drafted the key recommendation questions in PICO format, engaged the systematic review teams and guideline methodologists (i.e. the Evidence Synthesis Group; ESG), as well as the members of the Guideline Development Group (GDG) and the External Review Group (ERG) (see below). In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the GDG meetings, drafted and finalized the guideline document, and will also manage the guideline dissemination, implementation and impact assessment. The members of the WHO Steering Group are listed in Annex 1.

2.3 Guideline Development Group (GDG)

For the development of these updated recommendations, 18 external experts and relevant stakeholders were invited to participate as members of the GDG. These individuals were drawn from a pool of approximately 50 experts and relevant stakeholders who constitute the WHO Maternal and Perinatal Health Guideline Development Group (MPH-GDG). Those 18 selected for the GDG were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to prevention and treatment of postpartum haemorrhage (PPH). One participant was selected to serve as a consumer representative.

The GDG members for these recommendations were also selected in a way that ensured geographic representation and gender balance, and there were no important conflicts of interest. Based on the documents prepared by the WHO Steering Group, the GDG appraised and interpreted the evidence, and formulated the final recommendations at two GDG meetings in September and October 2018. The group also reviewed and approved the final guideline document. The members of this group are listed in Annex 1.

2.4 Evidence Synthesis Group (ESG)

WHO convened an ESG composed of guideline methodologists and systematic review teams to conduct or update systematic reviews, appraise the evidence and develop the Evidence to Decision frameworks.

Technical experts from Centro Rosarino de Estudios Perinatales (CREP) in Rosario, Argentina, and from the Cochrane Pregnancy and Childbirth (CPC) in Liverpool, the United Kingdom of Great Britain and Northern Ireland, served as the guideline methodologists. In relation to quantitative evidence on the effects of different prioritized interventions, the CPC provided input on the scoping of the priority questions and supervised the updating of relevant systematic reviews following the standard processes of the Cochrane Collaboration. The WHO Steering Group collaborated with the review authors on the updating of a Cochrane systematic review and network meta-analysis on uterotonics for the prevention of PPH *(19)* – the primary source of evidence on the effects (benefits and harms) of the intervention for all priority questions (listed in Table 3). The guideline methodologists from CREP and CPC appraised the evidence using the GRADE methodology *(20)*.

New systematic reviews of qualitative and cost-effectiveness studies were commissioned to generate evidence for other domains of the GRADE Evidence to Decision (EtD) frameworks (see section 2.8.2). Researchers from the University of Central Lancashire, United Kingdom, conducted a systematic review of qualitative studies related to women's and health care providers' views and experiences on interventions for the prevention of PPH *(21)*. An independent research consultant from Evidence-based Medicine Consultancy in Bath, United Kingdom, led the work of conducting a systematic review of cost-effectiveness studies on uterotonics for PPH prevention *(22)*. These reviews were conducted in collaboration with the WHO Steering Group, whose members worked closely with all members of the ESG to review the evidence and prepare the GRADE EtD frameworks. All members of the ESG attended the GDG meetings to provide an overview of the synthesized evidence, and to respond to technical queries from the GDG. The members of the ESG are listed in Annex 1.

2.5 Observers

Representatives of the United States Agency for International Development (USAID), Jhpiego, the Bill & Melinda Gates Foundation, the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and Gynuity Health Projects participated in the GDG meetings as observers. These organizations, with their long history of collaboration with the relevant WHO departments in guideline dissemination and implementation, were identified as potential implementers of the recommendations. The list of observers who participated in the GDG meetings is included in Annex 1.

2.6 External Review Group (ERG)

The ERG included eight technical experts with interests and expertise in the provision of evidence-based care to prevent and treat PPH. The group was geographically diverse and gender balanced, and the members had no important conflicts of interest. The experts reviewed the final document to identify any factual errors, and commented on the clarity of language, contextual issues and implications for implementation. They ensured that the decision-making processes had considered and incorporated contextual values and the preferences of persons affected by the recommendations, health care professionals and policy-makers. It was not within the remit of this group to change the recommendations that were formulated by the GDG. Members of the ERG are listed in Annex 1.

2.7 Identification of priority questions and outcomes

The priority questions for updating these recommendations were identified by the Executive GSG through a systematic prioritization process in 2017 *(11)*. The recommendations on uterotonics for PPH prevention were prioritized for updating primarily on the basis of the anticipated impact of ongoing trials relating to the research questions which underpinned these recommendations.

The priority outcomes were aligned with those from the 2012 *WHO recommendations on prevention and treatment of postpartum haemorrhage (13)*. These outcomes were initially

identified through a search of scientific databases for relevant, published systematic reviews and a prioritization of outcomes by the GDG for the 2012 guideline. After due consideration of the recently published core outcome set for prevention and treatment of PPH *(23)*, three additional outcomes – shock, maternal well-being and maternal satisfaction – were included for this update to ensure that evidence synthesis and recommendation decision-making by the GDG were driven by outcomes that are important to women, and to ensure that the final set of recommendations would be woman-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendations. The list of priority outcomes is provided in Annex 2.

2.8 Evidence identification and retrieval

Evidence to support this update was derived from several sources by the ESG (see section 2.4) working in collaboration with the WHO Steering Group.

2.8.1 Evidence on the effects of uterotonics

As mentioned, evidence on the effects (harms and benefits) of uterotonics for these recommendations was mainly derived from an updated Cochrane systematic review with a network meta-analysis *(19)*. The WHO Steering Group, in collaboration with the guideline methodologists, first determined that the existing Cochrane review with its network meta-analysis addressed all the prioritized questions. The systematic review, published in April 2018 in the Cochrane Library, had been prepared in accordance with standard procedures for preparing Cochrane reviews, based on studies identified from searches of the CPC Trials Register.[1] But in view of new evidence emerging from a large randomized controlled trial comparing oxytocin with carbetocin for PPH prevention *(24)*, and other trials relating to other uterotonics, the review authors were invited to update this Cochrane review following the standard Cochrane methodology and with the support of CPC staff and the WHO Steering Group.

The updated review included all randomized controlled trials of the effects of uterotonic drugs for the prevention of PPH. Trials that used any of the uterotonic agents of interest in women following a vaginal birth or a caesarean section, in hospital or community settings, were eligible. Trials were included if they administered uterotonic agents of any dosage, route or regimen systemically at birth for preventing PPH, and compared them against other uterotonic agents, placebo or no uterotonic agent. The review authors screened the search results, identified studies relevant to the priority questions and extracted data from eligible trials on priority outcomes and comparisons; these data were exported into STATA and Review Manager (RevMan) software for analysis. For the comparisons of interest (uterotonic options versus placebo, no treatment or other uterotonic options), the STATA and RevMan files were customized to reflect the key comparisons and priority outcomes and to determine effect estimates. STATA software was used to generate indirect and network effect estimates.

An additional search of the Cochrane Database of Systematic Reviews was conducted to identify any existing Cochrane reviews that also provided pairwise comparisons for the priority outcomes, to complement the findings of the Cochrane systematic review with the network meta-analysis *(19)*. Where considered necessary, additional evidence from separate reviews was used to assess the differential effects of different doses and/or routes of administration for individual uterotonic agents, or their use in different contexts *(25–30)*.

[1] The Cochrane Pregnancy and Childbirth (CPC) Trials Register is maintained by the CPC's Trial Search Coordinator and contains trials identified from: monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); weekly searches of MEDLINE; weekly searches of Embase; hand-searches of 30 journals and the proceedings of major conferences; weekly "current awareness" alerts for a further 44 journals; and monthly BioMed Central email alerts. For further information, see: http://pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register. In addition, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) were searched for unpublished, planned and ongoing trial reports using key search terms.

2.8.2 Evidence on values, resource use and cost-effectiveness, equity, acceptability and feasibility

For questions relating to other domains of the GRADE EtD frameworks (other than "effects"), new systematic reviews were commissioned from external experts. The external experts were asked to prepare a standard protocol before embarking on the review, including: (i) a clear and focused question; (ii) criteria for identification of studies, including search strategies for different bibliographic databases; (iii) methods for assessing risk of bias; and (iv) a data analysis plan. Each protocol was reviewed and endorsed by the WHO Steering Group before the respective review teams embarked on the review process. The entire systematic review development process was iterative, with the review teams in constant communication with the WHO Steering Group to discuss challenges and agree on solutions.

In this regard, a new qualitative systematic review was conducted on the views and experiences of women and health care providers on interventions for the prevention of PPH *(21)*. This review was the primary source of evidence on acceptability, feasibility and equity as they relate to the EtD frameworks for the uterotonic agents of interest. The search strategies for evidence identification and retrieval for these reviews can be found in the review protocol *(31)*. Evidence for these domains was also supplemented by findings from a qualitative systematic review on women's views and experiences during intrapartum care *(32)*.

Evidence on resource use and cost-effectiveness was based on a systematic review of the literature *(22)*. The review aimed to evaluate all available evidence regarding which uterotonic agents are cost-effective when used for preventing PPH, according to mode of birth and birth settings. Eligible studies were identified from the following databases from 1980 up to June 2018: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and the National Health Services Economic Evaluation Database (NHS EED). Additional eligible studies were also identified from the reference lists of eligible studies identified via searches of these databases. Eligible studies included those evaluating costs and cost-effectiveness of the uterotonic agents of interest (alone or in combination) in comparison with standard care, placebo or another uterotonic agent for the prevention of PPH in women in the third stage of labour, in any setting. Unit costs were extracted, as well as measures of costs, incremental costs and incremental cost-effectiveness.

Studies included in the review were conducted in Colombia, Ecuador, India, Malaysia, Mexico, Peru, Senegal, Uganda, the United Kingdom and the United Republic of Tanzania. One of the studies was an international study with a hypothetical cohort. To assess cost-effectiveness, studies adopted the perspective of the relevant national health system, except for one study which adopted a WHO perspective. The majority of the studies were model-based, using decision analytical models (decision trees). Various measures – both condition-specific and generic – were used to measure health outcomes relevant to the use of uterotonics, including incidence and cases of PPH, use of additional uterotonics, mortality, probability of mortality, referral to a higher-level health facility, adverse effects, quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). One study was a cost-effectiveness analysis of several uterotonics based on a network meta-analysis adopting a United Kingdom perspective. Six studies evaluated the cost-effectiveness of misoprostol versus management of the third stage of labour without any uterotonics (five studies) or oxytocin (one study), all of which were conducted in settings with low access to facility-based births. A further eight studies evaluated the cost-effectiveness of carbetocin versus oxytocin across various health care facility settings.

Findings were synthesized according to the context of use of uterotonics (hospital or community settings; vaginal or caesarean birth). Additionally, these domains were supplemented by an ongoing cost-of-care assessment of PPH at hospitals in four low- and middle-income countries that participated in the WHO carbetocin trial *(24)*, as well as by publicly available prices of uterotonic options in selected countries.

2.9 Quality assessment and grading of the evidence

2.9.1 Quality assessment of primary studies included in the reviews

The assessment of the quality of individual studies included in the Cochrane systematic review and network meta-analysis *(19)* followed a specific and explicit method of risk-of-bias assessment using six standard criteria outlined in the *Cochrane handbook for systematic reviews of interventions (33)*. Each included study was assessed and rated by reviewers as being at low, high or unclear risk of bias for sequence generation, allocation concealment, blinding of study personnel and participants, attrition, selective reporting and other sources of bias, such as publication bias. The assessment along these domains provided an overall risk of bias assessment for each included study, which indicates the likely magnitude and direction of the bias and how it is likely to impact the review findings.

Studies identified in the qualitative systematic review *(21)* were subjected to a quality appraisal system using a validated instrument that rated studies against 11 predefined criteria and then allocated a score to each of them ranging from A to D, with D indicating the presence of significant flaws that are very likely to affect the credibility, transferability, dependability and/or confirmability of the study. Studies scoring D were excluded on grounds of poor quality *(34)*. The quality of included studies on cost-effectiveness was assessed using the Consensus Health Economic Criteria (CHEC) tool *(35)*.

2.9.2 Quality assessment of the review evidence

The GRADE Working Group's approach for rating the quality of evidence in a network meta-analysis was used for rating the quality of effect estimates for the comparisons of interest *(36,37)*. The appraisal of quality for direct, indirect and network evidence was performed sequentially, in that order. First, the quality of direct evidence for a given outcome, where available, was rated using the standard GRADE approach based on consideration of study design limitations (risk of bias), inconsistency, imprecision, indirectness and publication bias *(12)*. Then the quality of the indirect evidence for the same outcome, where available, was determined based on the lower of the quality ratings of the "first-order" loop in the network diagram for this outcome. The final step was the determination of the quality of network evidence based on: (i) the higher of the quality ratings for direct and indirect evidence; (ii) whether the relevant network diagram exhibited "intransitivity", i.e. whether all the comparisons contributing data to the estimate were directly consistent with the PICO question; (iii) consideration of coherence between direct and indirect effect estimates; and (iv) precision of the network effect estimate (where the network estimate was precise, and the direct and/or indirect evidence contributing to the quality ratings were not, the quality of the network evidence was upgraded by one level for precision).

The certainty of network evidence for each outcome was rated as "high", "moderate", "low" or "very low", as defined according to the GRADE approach, indicated by the following statements.

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

After the certainty of evidence had been rated, Summary of Findings (SoF) tables were prepared. These included the effect estimates and quality judgements for each outcome from direct evidence, indirect evidence and the network meta-analysis, and an overall judgement of quality for each outcome based on the network estimate. The SoF tables were prepared for all comparisons (each uterotonic option versus placebo or no uterotonic, and uterotonic options versus oxytocin as the reference uterotonic). For each comparison of a uterotonic option versus placebo/no uterotonic, the corresponding SoF table included all priority outcomes. However, for comparisons of uterotonic options versus oxytocin, SoF tables were prepared by outcome, for ease of interpretation of their comparative effects.

The findings of the qualitative reviews were appraised for quality using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool *(38)*. The GRADE-CERQual tool, which uses a similar conceptual approach to other GRADE tools, provides a transparent method for assessing and assigning the level of confidence that can be placed in evidence from reviews of qualitative research. The systematic review team used the GRADE-CERQual tool to assign a level of confidence (high, moderate, low, very low) to each review finding according to four components: methodological limitations of the individual studies; adequacy of data; coherence; and relevance to the review question of the individual studies contributing to a review finding. Findings from individual cost-effectiveness studies were reported narratively for each comparison of interest.

2.10 Formulation of recommendations

The WHO Steering Group supervised and finalized the preparation of SoF tables and narrative evidence summaries in collaboration with the Evidence Synthesis Group (ESG) using the GRADE EtD framework *(39)*. EtD frameworks include explicit and systematic consideration of evidence on prioritized interventions in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. For each priority question, judgements were made on the impact of the intervention on each domain, in order to inform and guide the decision-making process. Using the EtD framework template, the WHO Steering Group and ESG created summary documents for each priority question covering evidence on each domain, as described below.

Effects: The evidence on the priority outcomes was summarized in this domain to answer the questions: "What are the desirable and undesirable effects of the uterotonic?" and "What is the certainty of the evidence on effects?" Where benefits clearly outweighed harms for outcomes that are highly valued by women, or vice versa, there was a greater likelihood of a clear judgement in favour of or against the uterotonic, respectively. Uncertainty about the net benefits or harms, or small net benefits, usually led to a judgement that did not favour the uterotonic or the comparator.

The higher the certainty of the evidence of benefits across outcomes, the higher the likelihood of a judgement in favour of the uterotonic. In the absence of evidence of benefits, evidence of potential harm led to a recommendation against the uterotonic. Where evidence of potential harm was found for uterotonics that were also found to have evidence of important benefits, depending on the level of certainty and the likely impact of the harm, such evidence of potential harm was more likely to result to a context-specific recommendation for the uterotonic, with the context explicitly stated within the recommendation.

Values: This domain relates to the relative importance assigned to the outcomes associated with the uterotonic by those affected, how such importance varies within and across settings, and whether this importance is surrounded by any uncertainty. The question asked was: "Is there important uncertainty or variability in how much women value the main outcomes associated with the uterotonic?" Uterotonics that resulted in outcomes that most women consistently value regardless of settings were more likely to lead to a judgement in favour of the uterotonic. This domain, together with the "effects" domain (see above), informed the "balance of effects" judgement.

Resources: For this domain, the questions asked were: "What are the resources associated with the uterotonic option?" and "Is the uterotonic option cost-effective?" The resources required to implement uterotonic use mainly include the costs of providing supplies, training, equipment and skilled human resources. A judgement in favour of or against the uterotonic was likely where the resource implications were clearly advantageous or disadvantageous, respectively. Cost evaluation relied on reported estimates obtained from the systematic review of cost-effectiveness studies *(22)*, prices of drug options, as well as the experiences and opinions of the GDG members.

Acceptability: For this domain, the question was: "Is the uterotonic acceptable to women and health care providers?" Qualitative evidence from the systematic reviews on women's and providers' views and experiences on PPH prevention *(21,32)* informed the judgements for this domain. The lower the acceptability, the lower the likelihood of a judgement in favour of the uterotonic.

Feasibility: The feasibility of implementing a uterotonic depends on factors such as the resources, infrastructure and training requirements, and the perceptions of health care providers responsible for administering it. The question addressed was: "Is it feasible for the relevant stakeholders to implement the uterotonic?" Qualitative evidence from the systematic reviews on women's and providers' views and experiences on PPH prevention *(21,32)* was used to inform judgements for this domain. Where major barriers were identified, it was less likely that a judgement would be made in favour of the uterotonic.

Equity: This domain encompasses evidence or considerations as to whether or not a uterotonic would reduce health inequities. Therefore, this domain addressed the question: "What is the anticipated impact of the uterotonic on equity?" The findings of qualitative systematic reviews on women's and providers' views and experiences *(21,32)*, the 2015 WHO report on inequalities in reproductive, maternal, newborn and child health *(40)*, as well as the experiences and opinions of the GDG members, were used to inform judgements for this domain. A uterotonic was likely to be recommended if its proven (or anticipated) effects reduce (or could reduce) health inequalities among different groups of women and their families.

For each of the above domains, additional evidence of potential harms or unintended consequences are described in the "additional considerations" subsections in the Web annexes. Such considerations were derived from studies that might not have directly addressed the priority question but which provided pertinent information in the absence of direct evidence. These were extracted from single studies, systematic reviews or other relevant sources.

The WHO Steering Group provided the EtD frameworks, including evidence summaries, SoF tables and other documents related to each recommendation, to GDG members two weeks in advance of the GDG meetings. The GDG members were asked to review and provide comments (electronically) on the documents before the GDG meetings. During the GDG meetings (11–12 September for consideration of Recommendations 1.1–1.6, and 3–4 October 2018 for consideration of Recommendations 2–4), which were conducted online under the leadership of the GDG chairperson, the GDG members collectively reviewed the EtD frameworks, the draft recommendations and any comments received through preliminary feedback. The purpose of the meetings was to reach consensus on each recommendation, including its direction and in some instances the specific context, based on explicit consideration of the range of evidence presented in each EtD framework and the judgement of the GDG members. The GDG classified each recommendation into one of the following categories.

- **Recommended:** This category indicates that the intervention should be implemented.
- **Not recommended:** This category indicates that the intervention should not be implemented.
- **Recommended only in specific contexts ("context-specific recommendation"):** This category indicates that the intervention is applicable only to the condition, setting or population specified in the recommendation, and should only be implemented in these contexts.
- **Recommended only in the context of rigorous research ("research-context recommendation"):** This category indicates that there are important uncertainties about the intervention. With this category of recommendation, implementation can still be undertaken on a large scale, provided that it takes the form of research that is able to address unanswered questions and uncertainties related both to effectiveness of the intervention or option, and its acceptability and feasibility.

2.11 Decision-making during the GDG meetings

The GDG meetings were guided by the following protocol: the meetings were designed to allow participants to discuss the supporting evidence and each of the recommendations drafted by the WHO Steering Group, and to reach a consensus on the final wording of each recommendation after revision. Consensus was defined as the agreement by three quarters or more of the GDG, provided that those who disagreed did not feel strongly about their position. Strong disagreements would have been recorded as such in this guideline document (there was no record of such disagreement at the GDG meetings). Where required, the GDG determined the context of recommendations by the same process of consensus, based on discussions about the balance of evidence on effects (benefits and harms) of the interventions across different contexts.

If the participants were unable to reach a consensus, the disputed recommendation, or any other decision, would be put to a vote. Voting would have been by a show of hands among members of the GDG. A recommendation or decision would stand if more than two thirds of the GDG voted in support of it, unless the disagreement was related to a safety concern, in which case the WHO Steering Group could choose not to issue a recommendation on the subject. WHO staff at the meetings, as well as the members of the ESG and the observers, were not eligible to vote. If the issue to be voted upon involved primary research or systematic reviews conducted by any of the participants who had declared an academic conflict of interest, those individuals would have been allowed to participate in the discussion, but not allowed to vote on the issue in question.

2.12 Management of declarations of interests

The disclosure and appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other non-WHO-staff experts and contributors is a critical part of guideline development at WHO. According to WHO regulations, all experts must declare their interests prior to participation in WHO guideline development processes and meetings. All GDG members were therefore required to complete a standard WHO Declaration of Interests (DOI) form before engaging in the guideline development process and before participating in the guideline-related meetings. A short biography of the GDG members was also published on the WHO Department of Reproductive Health and Research website for more than four weeks for public review and comments prior to the first GDG meeting. The WHO Steering Group reviewed all declarations before finalizing the experts' invitations to participate. Where any potential conflict of interest was declared, the WHO Steering Group determined whether such conflicts were serious enough to affect an expert's objective judgement in the course of the guideline and recommendation

development process. To ensure consistency, the Steering Group applied the criteria for assessing the severity of conflicts of interest as outlined in the *WHO handbook for guideline development to all participating experts (12).* All findings from the DOI statements received were managed in accordance with the WHO DOI guidelines on a case-by-case basis and communicated to the experts. Where a conflict of interest was not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, the experts were only required to openly declare the conflict of interest at the beginning of the GDG meeting and no further actions were taken. Annex 3 shows a summary of the DOI statements and how conflicts of interest declared by invited experts were managed by the WHO Steering Group.

2.13 Document preparation and peer review

The WHO Steering Group prepared draft versions of the EtD frameworks, which were made available to the participants two weeks before the meetings for their comments. During the meetings, these documents were modified in line with the participants' deliberations and remarks. Following the meetings, members of the WHO Steering Group drafted a full guideline document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members for their review and approval. The final document was also sent to eight external (non-WHO) independent experts (the ERG; see section 2.6) for peer review. The WHO Steering Group evaluated the inputs of the ERG peer-reviewers for inclusion in this document. After the meetings and external peer reviews, the modifications made to the document by the WHO Steering Group and editors consisted only of the correction of factual errors and improving language to address any lack of clarity.

3. Recommendations and supporting evidence

The Guideline Development Group (GDG) adopted four main recommendations and six sub-recommendations at the GDG meetings. This section outlines the recommendations corresponding to the priority questions listed in Table 3. To ensure that the recommendations are correctly understood and appropriately implemented in practice, additional "remarks" summarizing relevant points from the GDG discussions are included under each recommendation.

The Summary of Findings (SoF) tables and Evidence to Decision (EtD) frameworks, presenting the balance between the desirable and undesirable effects, values of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity issues that were considered in formulating each recommendation, are presented separately in the Web annexes to this document. In section 3.2 below, where the recommendations are presented, in the justification for each recommendation, a link is provided to the Web annex which presents the corresponding SoF tables: Web annexes 1–6 for Recommendations 1.1–1.6, and Web annex 7 for Recommendations 2, 3 and 4.

3.1 Guiding principles

The GDG agreed that the following overarching principles are applicable to all recommendations. These principles were consensus based, and were not directly derived from a systematic process of evidence retrieval, synthesis and grading. They are intended to underscore the importance of respect for women's rights, choices and dignity as recipients of care, and the need to maintain high ethical and safety standards in clinical practice. As highlighted in the WHO framework for the quality of maternal and newborn health care *(41)*, experience of care is as important as clinical care provision for achieving the desired person-centred outcomes. It is critical for health care stakeholders to ensure that all pregnant women receive relevant information from technically competent health care providers who are sensitive to their needs, willing to engage in shared decision-making and respectful of women's choices and preferences *(32)*.

These principles are not by themselves specific recommendations but are expected to guide end-users in the process of adapting and implementing the guideline in a range of contexts and settings.

- Application of the recommendations should be based on consideration of the general condition of the woman and her baby, her wishes and preferences, and respect for her dignity and autonomy, even in situations where her choices go against the advice of the care provider.
- Women should be counselled in advance on the need to use a uterotonic to prevent postpartum haemorrhage (PPH), the available uterotonic options, and their possible side-effects.
- Women should not be left unattended during the third stage of labour.
- In order to ensure that a uterotonic is effective, it is essential that health systems ensure that good-quality medicines are available wherever maternity services are provided.

3.2 Recommendations

3.2.1 Efficacy and safety of uterotonics for prevention of postpartum haemorrhage (PPH)

RECOMMENDATION 1

The use of an effective uterotonic for the prevention of PPH during the third stage of labour is recommended for all births. To effectively prevent PPH, only *one* of the following uterotonics should be used:

- **oxytocin (Recommendation 1.1)**
- **carbetocin (Recommendation 1.2)**
- **misoprostol (Recommendation 1.3)**
- **ergometrine/methylergometrine (Recommendation 1.4)**
- **oxytocin and ergometrine fixed-dose combination (Recommendation 1.5).**

Justification

- When used for PPH prevention, oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, and a fixed-dose combination of oxytocin and ergometrine demonstrated clinical benefits especially in terms of PPH reduction compared with no uterotonics. Although they all have variable undesirable effects, ranging from minor to significant, the Guideline Development Group (GDG) agreed that these undesirable effects do not outweigh the clinical benefits for any of these uterotonic options when considered in the context of not using any uterotonic. Evidence suggests that there is probably no important variability in, or uncertainty about, how much women value the health outcomes associated with these uterotonics. In spite of the differences in resource requirements, acceptability and feasibility of implementing the individual uterotonic options (as presented below), the GDG placed its emphasis on avoiding PPH and its complications where any of these uterotonic options is all that is available for care, and therefore recommended that any of these options can be applied for PPH prevention.

Remarks

- This recommendation applies to women undergoing a vaginal birth or caesarean section. For injectable uterotonics, skilled health personnel who are trained to administer them are required.
- To maximize efficacy, uterotonics are best given immediately (preferably within one minute) after the birth of the baby or babies. Administration of a uterotonic for prevention of PPH need not impede the delaying of cord clamping, as recommended by WHO *(13)*.
- The GDG advised that all women are to be provided with information – ideally during antenatal care – on the need for an effective uterotonic to prevent PPH.

RECOMMENDATION 1.1

The use of oxytocin (10 IU, IM/IV) is recommended for the prevention of PPH for all births. *(Recommended)*

Justification

- When used for PPH prevention, oxytocin is associated with a substantial reduction in PPH (≥ 500 ml), severe PPH (≥ 1000 ml), blood transfusion and the use of additional uterotonics when compared with placebo or no uterotonic. In the same context, oxytocin makes little or no difference to the risks of experiencing side-effects commonly associated with uterotonics, including nausea, vomiting,

abdominal pain, headache, hypertension, shivering, fever or diarrhoea. There is probably no important variability in, or uncertainty about, how much women value the health outcomes associated with oxytocin. Although there is no direct evidence, oxytocin is probably cost-effective because it is inexpensive and is associated with substantial clinical benefits and minimal side-effects. It is widely available in all settings at a low cost and probably increases health equity. While the currently available injectable form is feasible to implement in most settings, its acceptability by health personnel may vary in different settings, due to inconsistent supplies, limited electricity for appropriate storage or lack of experienced staff.

- The narrative evidence supporting this recommendation and the corresponding Summary of Findings (SoF) table can be found in **Web Annex 1**.

Remarks

- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required.
- The GDG noted that, to effectively prevent PPH and avoid potentially harmful haemodynamic side-effects at caesarean section, there was insufficient evidence from randomized controlled trials to recommend one oxytocin regimen over another. The group agreed that, in view of a number of observational studies suggesting dose-related side-effects (particularly hypotension and tachycardia), and potential effectiveness of oxytocin at doses much lower than 10 international units (IU), consideration needs to be given to dividing the recommended 10 IU dose between a smaller intravenous (IV) bolus and an infusion. A rapid IV bolus injection must be avoided. The GDG considered the identification of the optimal regimen of IV oxytocin at caesarean section to be an important research priority.
- For local adaptation of this recommendation as it applies to caesarean section, health systems need to ensure that adequate human resources exist to implement feasible IV oxytocin dosing strategies, without compromising the woman's safety. Personnel administering oxytocin at caesarean section must be alert to the potential haemodynamic side-effects associated with IV oxytocin use, exercise caution in its administration, and be prepared to provide effective resuscitation therapy should the need arise.
- Oxytocin is relatively inexpensive and widely available; however, it requires refrigerated transport and storage (2–8 °C) *(42)*. In settings where this cannot be guaranteed, the quality and effectiveness of oxytocin may be adversely affected. In these situations, another effective uterotonic may be considered.

RECOMMENDATION 1.2

The use of carbetocin (100 μg, IM/IV) is recommended for the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics.
(Context-specific recommendation)

Justification

- When used for PPH prevention, carbetocin is associated with a substantial reduction in PPH (≥ 500 ml), severe PPH (≥ 1000 ml), blood transfusion and the use of additional uterotonics when compared with placebo or no uterotonic. It makes little or no difference to the risks of experiencing side-effects such as nausea, abdominal pain, headache, shivering and fever. There is probably no important variability in, or uncertainty about, how much women value the health outcomes associated with carbetocin. However, it is currently not available in all settings – and where it is available, the current unit cost is high. There is no direct evidence to suggest that carbetocin is cost-effective in settings where the cost of PPH care

is moderate. Given the substantial beneficial effects and minimal side-effects, carbetocin would probably be cost-effective if the unit cost is comparable to other effective uterotonics and in settings where the cost of PPH care is substantial. Carbetocin in the current injectable form is feasible to implement as its heat-stable formulation does not require cold chain transport or refrigerated storage. However, its acceptability and impact on equity would vary across settings as the current unit cost is high.

- The contextual nature of this recommendation was informed by the current cost of using carbetocin for PPH prevention, which surpasses that of other effective uterotonics. While acknowledging that carbetocin may be cost-effective in some high-income settings (where the cost of managing PPH and its complications is high), the GDG placed its emphasis on the uncertainties regarding its cost-effectiveness in lower-income settings, where effective and cheaper uterotonic options are available. However, the GDG noted that this consideration may change on the basis of a signed memorandum of understanding between WHO and the manufacturer to make the heat-stable formulation of carbetocin available in public sector health care facilities in low- and low-middle income countries at an affordable and sustainable price (comparable to the United Nations Population Fund [UNFPA] price of oxytocin) *(24)*.
- The narrative evidence supporting this recommendation and the corresponding SoF table can be found in **Web Annex 2**.

Remarks

- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required.
- This recommendation applies only to the use of carbetocin for the prevention of PPH. Carbetocin is not currently recommended for other obstetric indications (such as labour induction, labour augmentation or treatment of PPH).
- The GDG noted that both heat-stable and non-heat-stable formulations of carbetocin are available. The heat-stable formulation differs from the non-heat-stable formulation only in its excipients *(24)*. Heat-stable carbetocin does not require refrigeration and therefore eliminates the costs associated with refrigerated storage and transport for non-heat-stable uterotonics.
- Previous trials of carbetocin have used both intramuscular (IM) and IV administration. A WHO multicountry trial of nearly 30 000 women used a regimen of 100 μg IM carbetocin (heat-stable formulation) in a range of high-, middle- and low-income settings.
- Previous trials of carbetocin have all been conducted in hospital settings. While the GDG acknowledged that the effectiveness of carbetocin in preventing PPH in community settings has not been evaluated in trials, the group agreed that there is no reason to expect differential effectiveness between hospital and community settings, provided that carbetocin is administered under similar conditions as other injectable uterotonics.

RECOMMENDATION 1.3

The use of misoprostol (either 400 μg or 600 μg, PO) is recommended for the prevention of PPH for all births. *(Recommended)*

Justification

- When used for PPH prevention, misoprostol is associated with a substantial reduction in PPH (≥ 500 ml), severe PPH (≥ 1000 ml), blood transfusion and the use of additional uterotonics when compared with placebo or no uterotonic. In the

same context, however, misoprostol substantially increases the risks of shivering, fever and diarrhoea, but makes little or no difference to other side-effects. There is probably no important variability in, or uncertainty about, how much women value the health outcomes associated with misoprostol. Overall, the balance of effects favours misoprostol as these side-effects are often self-limiting. As it is inexpensive and can also be used by lay health workers in community settings, it is associated with moderate savings and is probably cost-effective, especially when implemented in settings with a shortage of skilled health personnel. It probably increases health equity as it can be applied by all health care worker cadres in any birth setting and thus increases coverage. Its acceptability may be limited in settings where providers have concerns regarding potential misuse, or where health care providers are in need of more information on its effectiveness and implementation.

- The narrative evidence supporting this recommendation and the corresponding SoF table can be found in **Web Annex 3**.

Remarks

- The GDG noted that evidence on the efficacy of misoprostol was largely derived from trials involving women having vaginal births. However, misoprostol has been used for women undergoing caesarean section in a few trials. The GDG emphasized that there may be a need for the use of alternative routes of administration, such as rectal for women under general anaesthesia for caesarean section, or rectal or sublingual for women under spinal anaesthesia for caesarean section.
- The GDG noted that previous trials have largely used 600 μg or 400 μg doses of misoprostol. While there is currently no clear evidence to demonstrate that a 600 μg dose provides greater efficacy over a 400 μg dose, there is some evidence that higher doses are likely to have worse side-effects.
- Although different routes of administration (i.e. oral, buccal, sublingual, rectal) have been evaluated in trials of misoprostol for PPH prevention, the recommended route of administration is based on the consideration of women's preferences for oral over rectal administration.
- Providers administering misoprostol need to ensure that women are aware of the possible adverse effects of misoprostol (including shivering, fever and diarrhoea), and must be prepared to manage these if they occur.
- Misoprostol for PPH prevention can be used in both hospital and community settings.

RECOMMENDATION 1.4

The use of ergometrine/methylergometrine (200 μg, IM/IV) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use. *(Context-specific recommendation)*

Justification

- When used for PPH prevention, ergometrine/methylergometrine is associated with substantial reductions in PPH (≥ 500 ml) and the use of additional uterotonics when compared with placebo or no uterotonic. However, it is also associated with side-effects including nausea, vomiting, hypertension, headache and abdominal pain. There is no evidence of uncertainty about how much women value the health outcomes associated with ergometrine/methylergometrine. Although ergometrine/methylergometrine in the injectable form is widely available and generally acceptable and feasible to use, its cost-effectiveness and impact on health equity are not known because of the increased likelihood of side-effects, particularly hypertension, which means that the presence of skilled health personnel is required for its safe use.

- The GDG placed its emphasis on the danger of the increased risk of hypertension (50 per 1000 births) associated with ergometrine/methylergometrine use and therefore made a context-specific recommendation. The group noted that women with underlying cardiovascular disorders may be prone to further exacerbation by ergot alkaloids.
- The narrative evidence supporting this recommendation and the corresponding SoF table can be found in **Web Annex 4**.

Remarks

- In the context of this recommendation, hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia.
- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required.
- Women need to be informed of the possible side-effects (including hypertension, nausea, headache, vomiting and abdominal pain) prior to use. Where other options are available, women may be offered the choice of an alternative uterotonic with a better side-effect profile.
- Ergometrine/methylergometrine is relatively inexpensive and widely available; however, it requires refrigerated transport and storage (2–8 °C). In settings where this cannot be guaranteed, the quality and effectiveness of ergometrine/methylergometrine may be adversely affected. In these situations, another effective uterotonic can be considered.

RECOMMENDATION 1.5

The use of a fixed-dose combination of oxytocin and ergometrine (5 IU/500 μg, IM) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use. *(Context-specific recommendation)*

Justification

- When used for PPH prevention, the fixed-dose combination of oxytocin and ergometrine demonstrated a substantial reduction in PPH (≥ 500 ml), severe PPH (≥ 1000 ml), blood transfusion and the use of additional uterotonics when compared with placebo or no uterotonic. However, it probably increases women's risk of experiencing nausea and vomiting and the impact on other side-effects ranges from substantial benefits to considerable harm. While there is no clear difference in the risk of hypertension when oxytocin plus ergometrine was compared with placebo or no uterotonic, the GDG expressed concern about the potential risk of hypertension associated with the ergometrine component of this combination. Nonetheless, the group agreed that the potential benefits of this combination outweigh the harms if hypertensive disorders can be excluded. Although there is no direct evidence, oxytocin plus ergometrine combination compared with no PPH prevention might be cost-effective because the desirable effects are substantial. The combination is probably acceptable to stakeholders given that the individual components are widely used and acceptable to health care providers. However, its feasibility may be restricted in settings with limited capacity for storage of heat-sensitive uterotonics, and it may reduce health equity where screening or care for hypertensive disorders in pregnancy is not possible.
- The narrative evidence supporting this recommendation and the corresponding SoF table can be found in **Web Annex 5**.

Remarks

- In the context of this recommendation, hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension, pre-eclampsia andeclampsia.
- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required.
- The majority of trials that evaluated the efficacy of this combination have used the synthetic, fixed-dose combination of oxytocin and ergometrine (5 IU/500 μg) IM.
- Oxytocin and ergometrine/methylergometrine require refrigerated transport and storage (2–8 °C). In settings where this cannot be guaranteed, the quality and effectiveness of ergometrine/methylergometrine may be adversely affected. In these situations, another effective uterotonic can be considered instead of this combination.

RECOMMENDATION 1.6

Injectable prostaglandins (carboprost or sulprostone) are not recommended for the prevention of PPH. *(Not Recommended)*

Justification

- When used for PPH prevention, injectable prostaglandins (carboprost and sulprostone) are not beneficial for substantive priority outcomes (severe PPH [≥ 1000 ml], blood transfusion and the use of additional uterotonics) except PPH (≥ 500 ml), for which they show a 39% risk reduction compared with placebo or no uterotonic. However, they are associated with increased risk of vomiting and diarrhoea. The associated risk of diarrhoea is particularly high with a number needed to harm (NNH) of 6. Injectable prostaglandins are currently not available in all settings and where they are available, the unit cost is high. While there is no direct evidence on cost analysis regarding these uterotonics compared to no uterotonics, they are probably not cost-effective because of lack of benefits for most priority outcomes and substantial side-effects. As they are not widely available and not routinely used for obstetric indications, their acceptability is not known and the feasibility of implementation in clinical practice would vary according to local availability. The potential costs of these uterotonics may prohibit access for women in disadvantaged regions and thus would probably reduce equity.
- The narrative evidence supporting this recommendation and the corresponding SoF table can be found in **Web Annex 6**.

Remarks

- Trials of systemic injectable prostaglandins for PPH prevention have used carboprost or sulprostone.
- Local administration of injectable prostaglandins, such as intrauterine injections during caesarean section, was not considered.
- This recommendation relates to the use of injectable prostaglandins for prevention of PPH only; it does not relate to the treatment of PPH.

3.2.2 Choice of uterotonics for prevention of postpartum haemorrhage

RECOMMENDATIONS 2, 3 and 4

Justifications

- When used for PPH prevention, oxytocin, carbetocin, misoprostol, ergometrine/methylergometrine, and a fixed-dose combination of oxytocin and ergometrine demonstrated variable clinical benefits and side-effects ranging from minor to significant when compared with one another. As oxytocin is the most widely used and most frequently investigated of all these uterotonics, different uterotonic options have been compared with oxytocin as the reference agent across all important considerations to determine the most efficacious uterotonic option with the best safety profile, which is also cost-effective, acceptable to stakeholders, feasible to implement and likely to increase health equity.
- Carbetocin has similar desirable effects compared with oxytocin, though it is likely to be superior to oxytocin in reducing PPH (≥ 500 ml) (41 fewer events per 1000 women), use of additional uterotonics (74 fewer per 1000 women) and blood loss after birth (81 ml less on average). The mean change in haemoglobin level (before versus after birth) may be smaller among women receiving carbetocin. There is no clear difference between carbetocin and oxytocin in terms of undesirable effects. While the balance of effects probably favours carbetocin, the supply cost of carbetocin is approximately 20 times more than oxytocin and it is uncertain whether the additional benefits justify the additional cost of routinely implementing carbetocin at the current unit price. As a consequence, acceptability among stakeholders and impact on health equity would vary across settings compared with oxytocin.
- Misoprostol has similar desirable effects to oxytocin, but it is less effective for reducing severe PPH (≥ 1000 ml) (7 more per 1000 women). Misoprostol causes more undesirable effects than oxytocin (including nausea, vomiting, shivering, fever and diarrhoea). While misoprostol is cheaper, heat-stable, can be used orally, and is probably acceptable and feasible to use, the lower effectiveness for severe PPH and greater undesirable effects may increase costs (these costs may vary according to the setting, depending on factors such as bed costs and the approach to managing these side-effects). Misoprostol has the advantage that it can be task-shifted to lay health workers and community health workers since it requires minimal training and no additional supplies for implementation.
- There is no clear evidence of any difference in desirable effects between ergometrine/methylergometrine and oxytocin when used for PPH prevention. However, women are more likely to experience nausea (143 more per 1000 women), vomiting (38 more per 1000), headache (152 more per 1000), hypertension (618 more per 1000) and diarrhoea (17 more per 1000) with ergometrine/methylergometrine. The costs associated with managing these undesirable effects, as well as the need to screen for high blood pressure, implies that oxytocin is probably more cost-effective. Ergometrine/methylergometrine may have negative effects on health equity in settings with high rates of – or lack of screening for – hypertensive disorders.
- The fixed-dose combination of oxytocin and ergometrine is similar to oxytocin in terms of desirable outcomes, though it is possibly more effective in preventing PPH (≥ 500 ml) (44 fewer per 1000). However, it has more undesirable effects than oxytocin, including nausea (105 more per 1000 women), vomiting (54 more per 1000) and diarrhoea (9 more per 1000). The balance of effects clearly favours oxytocin. The costs related to managing associated undesirable effects, as well as the need to screen for women with hypertensive disorders due to concern regarding

the ergometrine component, imply that oxytocin is probably more cost-effective. Compared with oxytocin alone, the combination of oxytocin and ergometrine may have a negative impact on health equity, particularly in settings with limited capacity and capability to routinely screening for hypertensive disorders of pregnancy.

- The combination of oxytocin plus misoprostol is probably superior to oxytocin alone in terms of blood transfusion (11 fewer per 1000), additional uterotonic use (58 fewer per 1000) and blood loss (88 ml less on average). The combination may possibly prevent more PPH (≥ 500 ml) (44 fewer per 1000) and result in a smaller mean change in haemoglobin level (before versus after birth) compared with oxytocin. However, this combination is associated with more undesirable effects than oxytocin, including nausea (90 more per 1000), vomiting (31 more per 1000), diarrhoea (12 more per 1000), shivering (238 more per 1000) and fever (62 more per 1000). In view of the substantial side-effects, the balance of effects favours oxytocin. Consequently, the cost-effectiveness of the combination may vary in different settings – costs may be reduced due to some improved desirable outcomes, but costs may increase for management of undesirable effects. The feasibility of the oxytocin plus misoprostol combination is limited due to the complexity of using two separate medications through different routes of administration.
- The narrative evidence supporting these recommendations and the corresponding SoF tables can be found in **Web Annex 7**.

RECOMMENDATION 2

In settings where multiple uterotonic options are available, oxytocin (10 IU, IM/IV) is the recommended uterotonic agent for the prevention of PPH for all births. *(Recommended)*

Remarks

- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required.
- The remarks for Recommendation 1.1 apply to this recommendation.
- While the GDG acknowledged that there is evidence that a combination of misoprostol and oxytocin may be more effective than oxytocin alone for some priority outcomes, there are concerns that this combination also increases important side-effects for the woman. As misoprostol and oxytocin are not available as a fixed-dose combination, and the two agents have to be administered through separate routes (parenteral and oral), the GDG considered the application of this combination less feasible when used routinely in clinical settings compared with using either oxytocin or misoprostol as a single agent. However, if the care provider and the parturient woman regard the additional benefits of a combination of misoprostol and oxytocin (over either of these agents alone) as important in improving overall maternal outcomes, the use of this combination could be considered.

RECOMMENDATION 3

In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics (carbetocin, or if appropriate ergometrine/methylergometrine, or oxytocin and ergometrine fixed-dose combination) or oral misoprostol is recommended for the prevention of PPH. *(Recommended)*

Remarks

- This recommendation applies to women undergoing a vaginal birth or caesarean section. Skilled health personnel who are trained to administer injectable uterotonics are required for carbetocin, ergometrine/methylergometrine or the fixed-dose combination of oxytocin and ergometrine.
- The GDG acknowledged recent evidence that oxytocin (as well as other uterotonics) in some settings may be of poor quality and would therefore be less effective or ineffective in preventing PPH. Health systems stakeholders need to ensure that the manufacture and cold-chain transport and storage of oxytocin is sufficiently rigorous to ensure good quality.
- The GDG emphasized that any other uterotonic agent that is considered as a potential alternative to oxytocin in the context of this recommendation needs to be quality certified. Where the quality of oxytocin is considered compromised due to inadequate cold-chain transport and storage conditions, heat-sensitive uterotonic agents such as ergometrine/methylergometrine or oxytocin and ergometrine fixed-dose combination, which have been transported and stored under similar conditions as the oxytocin, are not suitable options either. In these situations, heat-stable uterotonic agents (heat-stable formulation of carbetocin or misoprostol) may be more suitable options, depending on the context.
- The recommended doses and routes of administration for these uterotonic options are:
  - carbetocin, 100 μg (IM/IV), in contexts where its cost is comparable to other effective uterotonics (see Recommendation 1.2);
  - misoprostol, either 400 μg or 600 μg (PO) (see Recommendation 1.3);
  - ergometrine/methylergometrine, 200 μg (IM/IV), in contexts where hypertensive disorders can be safely excluded prior to its use (see Recommendation 1.4); and
  - oxytocin and ergometrine fixed-dose combination, 5 IU/500 μg (IM), in contexts where hypertensive disorders can be safely excluded prior to its use (see Recommendation 1.5).

RECOMMENDATION 4

In settings where skilled health personnel are not present to administer injectable uterotonics, the administration of misoprostol (either 400 μg or 600 μg, PO) by community health workers and lay health workers is recommended for the prevention of PPH. *(Recommended)*

Remarks

- Skilled health personnel who provide care during childbirth are defined by the 2018 joint statement by WHO, the United Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF), the International Confederation of Midwives (ICM), the International Council of Nurses (ICN), the International Federation of Gynecology and Obstetrics (FIGO) and the International Pediatric Association (IPA)

as competent maternal and newborn health (MNH) professionals who hold identified MNH competencies; are educated, trained and regulated to national and international standards; and are supported within an enabling environment in the health system *(6)*.

- The GDG acknowledged that there are settings where skilled health personnel may not be present, or where they may not have been trained to administer injectable uterotonics appropriately. In these settings, oral misoprostol would be the preferred uterotonic.

4. Dissemination and implementation of the recommendations

The dissemination and implementation of these recommendations is to be considered by all stakeholders involved in the provision of care for pregnant women at the international, national and local levels. There is a vital need to increase women's access to maternal heath care, and strengthen the capacity at health care facilities of all levels to ensure they can provide high-quality services to all women giving birth. It is therefore crucial that these recommendations be translated into care packages and programmes at country and health care facility levels, where appropriate.

4.1 Dissemination and evaluation

A shorter document containing the recommendations, remarks, implementation considerations and research priorities will be prepared for public dissemination. This shorter document will have annexes (also made publicly available) containing all the information in this document, including methods, Evidence to Decision (EtD) frameworks and Summary of Findings (SoF) tables, for reference as needed. The WHO Steering Group will also develop derivative tools to aid understanding and adaptation of these recommendations to local contexts, including a policy brief on postpartum haemorrhage (PPH) prevention, an updated PPH prevention clinical algorithm and an online interactive platform on PPH prevention. The recommendations and derivative tools will be disseminated through WHO regional and country offices, ministries of health, professional organizations, WHO collaborating centres, other United Nations agencies and nongovernmental organizations, among others. The recommendations will be published in the WHO Reproductive Health Library (RHL; available at: www.who.int/rhl) and on the WHO Department of Reproductive Health and Research website as part of the monthly HRP News.[1] This site currently has over 4500 subscribers, including clinicians, health programme managers, policy-makers and service users from all around the world. Updated recommendations are also routinely disseminated during meetings and scientific conferences attended by WHO maternal and perinatal health staff.

The executive summary and recommendations from this publication will be translated into the six United Nations languages for dissemination through the WHO regional and country offices and during meetings organized by, or attended by, staff of the WHO Department of Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health. Technical assistance will be provided to any WHO regional office willing to translate these recommendations into any of the languages.

In addition, a number of articles presenting the recommendations and key implementation considerations will be published, in compliance with WHO's open access and copyright

[1] Available at: https://www.who.int/reproductivehealth/news/en/ (scroll down for a link to subscribe)

policies. Relevant WHO clusters, departments and partnerships, such as the Partnership for Maternal, Newborn & Child Health (PMNCH), will also be part of this dissemination process.

In order to ensure these recommendations have impact on maternal and perinatal health at the country level, coordinated action between international agencies, national departments of health and key maternal and perinatal health stakeholders is needed. National and subnational working groups should assess current national guidelines and protocols, and determine whether development of new guidelines or updating of existing guidelines is required in line with these new WHO recommendations. WHO staff at the headquarters, regional and country levels, as well as international agency partners and international professional societies (such as FIGO and ICM), and national professional associations, can support national stakeholders in developing or revising existing national guidelines or protocols, and optimizing their implementation.

4.2 Implementation considerations

- The successful introduction of evidence-based policies related to the prevention and management of PPH into national health programmes and health care services depends on well planned, participatory and consensus-driven processes of adaptation and implementation. These processes may include the development or revision of national guidelines or protocols based on these recommendations, and engagement with all relevant stakeholder groups, including skilled health personnel.
- The recommendations should be adapted into documents and tools that are appropriate for different locations and contexts, to meet the specific needs of each country and health service. Modifications to the recommendations, where necessary, should be justified in an explicit and transparent manner.
- An enabling environment should be created for the implementation of these recommendations, including education to support behaviour change among skilled health personnel to facilitate the use of evidence-based practices.
- National health systems need to ensure that supplies of good-quality uterotonics and the necessary equipment are available wherever maternity services are provided. This includes establishing robust and sustainable regulatory, procurement and logistics processes that can ensure good-quality medicines and equipment are obtained, transported and stored correctly.
- In order to implement these recommendations, skilled health personnel working in settings where women give birth require training and supportive supervision in how to use uterotonics appropriately and safely, and how to inform and counsel women on the risks and benefits of the available uterotonics. In settings where a new uterotonic is introduced (or where recommended practices are changed), additional training and monitoring may be required. Special attention needs to be given to correct dosage and safe use of uterotonics for PPH prevention, and efforts are needed to ensure that uterotonics are not mis-used for other indications.
- In settings where task shifting has been introduced for the administration of uterotonics to prevent PPH, it is advised that health care stakeholders consider the needs of the relevant cadres who are administering uterotonics to women (such as community health workers or lay health workers), including the need for drug supplies, access to functioning referral systems, training and supervision *(43)*.
- Local professional societies and training institutions can play an important role in implementation, and an all-inclusive and participatory process should be encouraged.
- Procurement agencies at all levels of supply chains should procure only quality-certified uterotonic medicines *(44)*. For example, those responsible for procurement of oxytocin should procure only quality-certified oxytocin, labelled for storage at 2–8 °C, in single-use ampoules or vials of 10 international units (IU). While some manufacturer labelling may seem to indicate that oxytocin is stable at room temperature, stability may not have

been tested in the much warmer conditions that may be prevalent in some countries, and different formulations have different stability characteristics. To prevent its degradation and to safeguard its quality, oxytocin should always be stored in refrigeration, regardless of labelling.

- As oxytocin and ergometrine (as single or combination agents) require refrigerated transport and storage (protected from light and stored at 2–8 °C) *(42,45)*, their use may be less feasible in settings with limited or inconsistent electricity. Misoprostol or the heat-stable formulation of carbetocin may be more feasible in such settings, provided that heat-stable carbetocin is available locally at a comparable cost to other effective uterotonics.
- Ergometrine/methylergometrine is contraindicated in women with hypertensive disorders, and hence can only be used in settings where women can be screened for these conditions. It may therefore be less feasible to use this option in settings with few skilled birth attendants and limited capacity for screening for hypertensive disorders of pregnancy.
- It is advised that programmes to implement uterotonics for PPH prevention ensure women are adequately informed in advance about the need to use a uterotonic to prevent PPH, the available uterotonic options, the possible side-effects of these options and their rights to choose what care they receive.

5. Research implications

The Guideline Development Group (GDG) identified important knowledge gaps that need to be addressed through primary research; further evidence in these areas may have an impact on the recommendations presented in this guideline.

The following questions were identified as high priority:

- What are the main outcomes that women (and their families) value in relation to interventions to prevent postpartum haemorrhage (PPH)?
- What are the effects of uterotonics for PPH prevention on other important outcomes, such as breastfeeding, maternal well-being and satisfaction, skin-to-skin contact and mother–baby bonding?
- What is the most effective dose and route of administration for uterotonics for the prevention of PPH, by mode of birth?
  - In particular, what is the optimal regimen of intravenous oxytocin for women undergoing caesarean section?
- What are the most effective strategies to promote sustainable use of uterotonics for PPH prevention?
- What is the cost-effectiveness of different uterotonic options for PPH prevention in low- and middle-income countries?

6. Applicability issues

6.1 Anticipated impact on the organization of care and resources

Implementing these evidence-based recommendations requires resources for sustainable procurement and storage of uterotonic drugs. The Guideline Development Group (GDG) noted that updating training curricula and providing training on the recommendations would increase their impact and facilitate their implementation. Standardization of care, by including these recommendations into existing intrapartum and immediate postpartum care packages, can encourage behaviour change in health care providers.

As part of efforts to implement these recommendations, health system stakeholders may wish to consider the following potential barriers to their application:

- lack of human resources with the necessary expertise and skills to implement, supervise and support recommended practices;
- lack of understanding of changes in recommended interventions among skilled care personnel and system managers;
- resistance of skilled care personnel to changing from the use of non-evidence-based to evidence-based practices;
- lack of infrastructure to support interventions (e.g. electricity and refrigeration for temperature-sensitive uterotonics);
- lack of essential equipment, supplies and medicines (e.g. needles, syringes, gloves and uterotonics);
- lack of effective mechanisms to identify women who are experiencing PPH, in order to trigger PPH management pathways; and
- lack of health information management systems designed to document and monitor recommended practices (e.g. patient records, registers).

Various strategies for addressing these barriers and facilitating implementation are provided under implementation considerations in section 4.

6.2 Monitoring and evaluating guideline implementation

The implementation and impact of these recommendations will be monitored at the health-service, country and regional levels, as part of broader efforts to monitor and improve the quality of maternal and newborn care. The WHO document *Standards for improving quality of maternal and newborn care in health facilities (41)* provides a list of prioritized input, output and outcome measures which can be used to define quality of care criteria and indicators, and which should be aligned with locally agreed targets. In collaboration with the monitoring and evaluation teams of the WHO Department of Reproductive Health and Research and the WHO Department of Maternal, Newborn, Child and Adolescent Health, data on country- and regional-level implementation of the recommendations will be collected and evaluated in the short to medium term to evaluate their impact on national policies of individual WHO Member States. Interrupted time series, clinical audits or criterion-based audits could be used to obtain the relevant data on the use of interventions contained in this guideline.

With regard to postpartum haemorrhage (PPH) prevention, WHO recommends that the coverage of prophylactic uterotonics be used as a process indicator for the monitoring and prevention of PPH *(13)*. The suggested "prophylactic uterotonic coverage indicator" is calculated as the number of women receiving prophylactic uterotonics during the third stage of labour divided by all women giving birth. This indicator provides an overall assessment of adherence to key recommendations included in this guideline. The use of other locally agreed and more specific indicators (e.g. the assessment of the use of specific uterotonics) may be necessary to obtain a more complete assessment of the quality of care related to the prevention and treatment of PPH. WHO has developed specific guidance for evaluating the

quality of care for severe maternal complications (including PPH) based on the near-miss and criterion-based clinical audit concepts *(46)*. Monitoring of the quality of uterotonic drugs available in low-resource settings may help guide skilled health personnel in selecting the most effective uterotonic option for PPH prevention in the context where they are working.

7. Updating the recommendations

The Executive Guideline Steering Group (GSG) convenes regularly to review WHO's current portfolio of maternal and perinatal health recommendations and to help WHO prioritize new and existing questions for recommendation development and updating. Accordingly, these recommendations will be reviewed and prioritized by the Executive GSG. In the event that new evidence that could potentially impact the current evidence base is identified, the recommendations will be updated. If no new reports or information are identified, the recommendations may be revalidated.

Any concern about the validity of any recommendation will be promptly communicated via the WHO Department for Reprodutive Health and Research website, and plans will be made to update the recommendation, as needed.

WHO welcomes suggestions regarding additional questions for inclusion in future updates of these recommendations. Please email your suggestions to mpa-info@who.int.

8. References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33. doi:10.1016/S2214-109X(14)70227-X.
2. Thirteenth general programme of work, 2019–2023 (Draft). Seventy-first World Health Assembly, 5 April 2018. Geneva: World Health Organization; 2018 (A71/4; http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_4-en.pdf, accessed 14 December 2018).
3. Transforming our world: the 2030 agenda for sustainable development. New York (NY): United Nations; 2015.
4. Office of the United Nations High Commissioner for Human Rights. Technical guidance on the application of a human rights-based approach to the implementation of policies and programmes to reduce preventable maternal morbidity and mortality. Human Rights Council, twentieth session. New York (NY): United Nations General Assembly; 2012 (A/HRC/21/22).
5. Tunçalp Ö, Were WM, MacLennan C, Oladapo OT, Gülmezoglu AM, Bahl R, et al. Quality of care for pregnant women and newborns – the WHO vision. BJOG. 2015;122(8):1045–9. doi:10.1111/1471-0528.13451.
6. World Health Organization (WHO), United Nations Population Fund (UNFPA), United Nations Children's Fund (UNICEF), International Confederation of Midwives (ICM), International Council of Nurses (ICN), International Federation of Gynecology and Obstetrics (FIGO), International Pediatric Association (IPA). Definition of skilled health personnel: the 2018 joint statement by WHO, UNFPA, UNICEF, ICM, ICN, FIGO and IPA. Geneva: World Health Organization; 2018 (www.who.int/reproductivehealth/publications/statement-competent-mnh-professionals/en/, accessed 6 December 2018).
7. Souza JP, Gülmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. Lancet. 2013;381(9879):1747–55. doi:10.1016/S0140-6736(13)60686-8.
8. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol. 2008;22(6):999–1012. doi:10.1016/j.bpobgyn.2008.08.004.
9. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clin Obstet Gynecol. 2010;53(1):147–56. doi:10.1097/GRF.0b013e3181cc406d.
10. Daru J, Zamora J, Fernández-Félix BM, Vogel J, Oladapo OT, Morisaki N, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Glob Health; 2018. p. e548–54. doi:10.1016/S2214-109X(18)30078-0.
11. Executive Guideline Steering Group for Updating WHO Maternal and Perinatal Health Recommendations (2017–2019). Geneva: World Health Organization; 2017 (http://www.who.int/reproductivehealth/publications/updating-mnh-recommendations/en/, accessed 5 December 2018).
12. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf, accessed 6 December 2018).

13. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf, accessed 5 November 2018).

14. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018;46(D1):D1074–82. doi:10.1093/nar/gkx1037.

15. Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, et al. PubChem Substance and Compound databases. Nucleic Acids Res. 2016;44(D1):D1202–13. doi:10.1093/nar/gkv951.

16. Alliance Pharmaceuticals. Syntometrine ampoules. In: electronic Medicines Compendium (eMC) [website]. Leatherhead, United Kingdom: Datapharm Communications Limited; 2016 (https://www.medicines.org.uk/emc/product/865/smpc, accessed 9 November 2018).

17. The international pharmacopoeia, seventh edition. Geneva: World Health Organization; 2017.

18. WHO model list of essential medicines (20th List). March 2017 (Amended August 2017). Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf, accessed 5 November 2018).

19. Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review). Cochrane Database Syst Rev. 2018;CD011689. doi: 10.1002/14651858.CD011689.pub3.

20. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6. doi:10.1016/j.jclinepi.2010.07.015.

21. Finlayson K, Downe S, Vogel JP, Oladapo OT. What matters to women and healthcare providers in relation to interventions for the prevention of postpartum haemorrhage: a qualitative systematic review. 2018 (unpublished).

22. Lawrie TA, Rogozinska E, Vogel JP, Oladapo OT. The cost-effectiveness of uterotonic agents to prevent postpartum haemorrhage: a systematic review. 2018 (unpublished).

23. Meher S, Cuthbert A, Kirkham JJ, Williamson P, Abalos E, Aflaifel N, et al. Core outcome sets for prevention and treatment of postpartum haemorrhage: an international Delphi consensus study. BJOG. 2018. doi:10.1111/1471-0528.15335.

24. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. N Engl J Med. 2018;379(8):743–52. doi: 10.1056/NEJMoa1805489.

25. Oladapo OT, Okusanya BO, Abalos E. Intramuscular versus intravenous prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2012;(2):CD009332.

26. Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012;(8):CD000494.

27. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2013;(10):CD001808.

28. Liabsuetrakul T, Choobun T, Peeyananjarassri K, Islam QM. Prophylactic use of ergot alkaloids in the third stage of labour. Cochrane Database Syst Rev. 2018;(6):CD005456.

29. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012;(4):CD005457.

30. Pantoja T, Abalos E, Chapman E, Vera C, Serrano VP. Oxytocin for preventing postpartum haemorrhage (PPH) in non-facility birth settings. Cochrane Database Syst Rev. 2016;(4):CD011491.

31. Finlayson K, Downe S, Oladapo O, Vogel JP. Views and experiences of women and healthcare providers on interventions for the prevention and treatment of postpartum haemorrhage: a qualitative systematic review (protocol). PROSPERO (International prospective register of systematic reviews). 2018:CRD42018103033 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=103033, accessed 14 December 2018).

32. Downe S, Finlayson K, Oladapo O, Bonet M, Gülmezoglu AM. What matters to women during childbirth: a systematic qualitative review. PLoS One. 2018;13(4):e0194906. doi:10.1371/journal.pone.0194906.

33. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011 (https://training.cochrane.org/handbook, accessed 14 December 2018).

34. Walsh D, Downe S. Appraising the quality of qualitative research. Midwifery. 2006;22(2):108–19. doi:10.1016/j.midw.2005.05.004.

35. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. Int J Technol Assess Health Care. 2005;21(2):240–5.

36. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ. 2014;349:g5630. doi:10.1136/bmj.g5630.

37. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol. 2018;93:36–44. doi:10.1016/j.jclinepi.2017.10.005.

38. Lewin S, Booth A, Glenton C, Munthe-Kaas H, Rashidian A, Wainwright M, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings: introduction to the series. Implementation Science. 2018;13(Suppl 1):2. doi:10.1186/s13012-017-0688-3.

39. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016. doi:https://doi.org/10.1136/bmj.i2016.

40. State of inequality: reproductive, maternal, newborn and child health. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/handle/10665/164590/9789241564908_eng.pdf, accessed 5 November 2018).

41. Standards for improving quality of maternal and newborn care in health facilities. Geneva: World Health Organization; 2016 (https://www.who.int/maternal_child_adolescent/documents/improving-maternal-newborn-care-quality/en/, accessed 6 December 2018).

42. Monographs: dosage forms: specific monographs: oxytocin injection (Oxytocini injectio). In: The international pharmacopoeia, seventh edition. Geneva: World Health Organization; 2017.

43. WHO recommendations: optimizing health worker roles to improve access to key maternal and newborn health interventions through task shifting. Geneva: World Health Organization; 2012 (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/978924504843/en/, accessed 6 November 2018).

44. Survey of the quality of medicines identified by the United Nations Commission on Life Saving Commodities for Women and Children, 2015. Geneva: World Health Organization; 2016 (http://apps.who.int/medicinedocs/en/m/abstract/Js23209en/, accessed 6 December 2018).

45. Monographs: pharmaceutical substances: ergometrine hydrogen maleate (Ergometrini hydrogenomaleas). In: The international pharmacopoeia, seventh edition. Geneva: World Health Organization; 2017.

46. Evaluating the quality of care for severe pregnancy complications: the WHO near-miss approach for maternal health. Geneva: World Health Organization; 2011 (http://www.who.int/reproductivehealth/publications/monitoring/9789241502221/en/, accessed 6 December 2018).

Annex 1. External experts and WHO staff involved in the preparation of the recommendations

WHO Steering Group

Fernando ALTHABE
Medical Officer
Department of Reproductive Health and Research

Maurice BUCAGU
Medical Officer
Department of Maternal, Newborn, Child and Adolescent Health

Olufemi OLADAPO
Medical Officer
Department of Reproductive Health and Research

Nathalie ROOS
Technical Officer
Department of Maternal, Newborn, Child and Adolescent Health

Özge TUNÇALP
Scientist
Department of Reproductive Health and Research

Joshua VOGEL
Consultant
Department of Reproductive Health and Research

Guideline Development Group

Oluwarotimi Ireti AKINOLA
President
Society of Gynaecology and Obstetrics in Nigeria (SOGON)
Abuja, Nigeria

Shubha ALLARD
Consultant Haematologist
NHS Blood & Transplant and Barts Health NHS Trust
London, United Kingdom of Great Britain and Northern Ireland (United Kingdom)

Melania Maria Ramos de AMORIM
Obstetrician and Gynaecologist
Instituto Paraibano de Pesquisa Professor Joaquim Amorim Neto and Instituto de Medicina Integral Professor Fernando Figueira
Paraiba, Brazil

Brendan CARVALHO
Chief of Obstetric Anesthesia
Professor of Anesthesiology, Perioperative and Pain Medicine
Stanford University Medical Center
Palo Alto, CA, United States of America (USA)

Catherine DENEUX-THARAUX
Perinatal epidemiologist
Obstetrical, Perinatal and Pediatric Epidemiology Research Team
Centre of Research in Epidemiology and Statistics Sorbonne, Inserm
Paris, France

Sue FAWCUS
Senior Scholar and Professor Emeritus
Department of Obstetrics and Gynaecology
University of Cape Town
Cape Town, South Africa

Caroline HOMER
Co-Program Director Maternal and Child Health
Burnet Institute
Melbourne, Australia

Simon LEWIN
Health systems researcher
Global Health Unit
Norwegian Institute of Public Health
Oslo, Norway

Tippawan LIABSUETRAKUL
Professor of Obstetrics and Gynecology
Epidemiology Unit, Faculty of Medicine
Prince of Songkla University
Songkhla, Thailand

Anita MAEPIOH
Nurse Educator
Department of Obstetrics and Gynaecology
National Referral Hospital
Honiara, Solomon Islands

Martin MEREMIKWU
Professor
Department of Paediatrics
University of Calabar
Calabar, Nigeria

Suellen MILLER
Director, Safe Motherhood Program
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco
San Francisco, CA, USA

Rintaro MORI
Director
Department of Health Policy and Department of Clinical Epidemiology
National Research Institute for Child Health and Development
Tokyo, Japan

Ashraf NABHAN (Chair)
Professor
Department of Obstetrics and Gynecology
Ain Shams University
Cairo, Egypt

Hiromi OBARA
Health Policy Advisor
Japan International Cooperation Agency (JICA)
Vientiane, Lao People's Democratic Republic

Rachel PLACHCINSKI
Research Engagement Officer, Knowledge Team
National Childbirth Trust (Charity)
London, United Kingdom

Hayfaa WAHABI
Professor and Chair
Evidence-based Healthcare and Knowledge Translation
College of Medicine, King Saud University
Riyadh, Saudi Arabia

Dilys WALKER
Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco
San Francisco, CA, USA

Evidence Synthesis Group

Edgardo ABALOS
Vice Director
Centro Rosarino de Estudios Perinatales (CREP)
Rosario, Argentina

Mónica CHAMILLARD
Medical Doctor
CREP
Rosario, Argentina

Virginia DIAZ
Obstetrician & Gynaecologist
CREP
Rosario, Argentina

Soo DOWNE
Professor
Midwifery Studies
University of Central Lancashire
Preston, Lancashire, United Kingdom

Kenneth FINLAYSON
Senior Research Assistant
Midwifery Studies
University of Central Lancashire
Preston, Lancashire, United Kingdom

Ioannis GALLOS
Clinician and Scientist
Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research
University of Birmingham
Birmingham, United Kingdom

Leanne JONES
Research Associate
Cochrane Pregnancy and Childbirth
University of Liverpool
Liverpool, United Kingdom

Frances KELLIE
Managing Editor
Cochrane Pregnancy and Childbirth
University of Liverpool
Liverpool, United Kingdom

Theresa LAWRIE
Director
Evidence Based Consultancy Ltd
Bath, United Kingdom

Argyro PAPADOPOULOU
Junior Clinical Fellow in Obstetrics and Gynaecology
Birmingham Women's Hospital
Birmingham, United Kingdom

Julia PASQUALE
Medical Doctor
CREP
Rosario, Argentina

Myfanwy WILLIAMS
Research Associate
Cochrane Pregnancy and Childbirth
University of Liverpool
Liverpool, United Kingdom

Observers

Deborah ARMBRUSTER
Senior Maternal and Newborn Health Advisor
United States Agency for International Development (USAID)
Center for Population, Health and Nutrition
Washington, DC, USA

Jerker LILJESTRAND
Senior Program Officer (Maternal, Newborn, Child Health)
Bill & Melinda Gates Foundation
Seattle, WA, USA

Jeffrey SMITH
Vice President, Technical Leadership
Jhpiego
Baltimore, MD, USA

Mary Ellen STANTON
Senior Reproductive Health Advisor
USAID
Washington, DC, USA

Sally TRACY
Professor of Midwifery
Representative, International Confederation of Midwives (ICM)
Sydney University
Sydney, Australia

Gerard H.A. VISSER
Chair, FIGO Committee on Safe Motherhood and Newborn Health
Representative, International Federation of Gynecology and Obstetrics (FIGO)
Department of Obstetrics
University Medical Center
Utrecht, Netherlands

Beverly WINIKOFF
President
Gynuity Health Projects
New York, NY, USA

External Review Group

Michel BOULVAIN
Professor
Department of Obstetrics and Gynaecology
Geneva University Hospital
Geneva, Switzerland

Jemima A. DENNIS-ANTWI
International consultant in Midwifery
West Legon
Accra, Ghana

Vanora HUNDLEY
Professor of Midwifery
Centre for Midwifery, Maternal and Perinatal Health
Bournemouth University
Bournemouth, United Kingdom

Tamar KABAKIAN-KHASHOLIAN
Associate Professor
Department of Health Promotion and Community Health
Faculty of Health Sciences
American University of Beirut
Beirut, Lebanon

Barbara LEVY
Vice-President for Health Policy
American College of Obstetricians and Gynecologists
Washington, DC, USA

Lawal O. OYENEYIN
Senior Lecturer and Acting Head
Department of Obstetrics and Gynaecology
University of Medical Sciences/ University of Medical Sciences Teaching Hospital
Ondo, Nigeria

Alison WRIGHT
Vice President for UK and Global Membership
Royal College of Obstetricians and Gynaecologists
London, United Kingdom

Qian XU
Professor
Department of Maternal, Child and Adolescent Health
School of Public Health, Fudan University
Shanghai, China

WHO country and regional offices

Nino BERDZULI
Regional Adviser
Sexual and Reproductive Health
Noncommunicable diseases and life-course
WHO Regional Office for Europe
Copenhagen, Denmark

Paata CHIKVAIDZE
Medical Officer
Maternal and Child Health
WHO Country Office – Afghanistan
Kabul, Afghanistan

Bremen DE MUCIO
Regional Advisor
Sexual and Reproductive Health
WHO Regional Office for the Americas
Montevideo, Uruguay

Hayfa ELAMIN
Technical Officer
WHO Country Office – Solomon Islands
Honiara, Solomon Islands

Fatu FORNA
Team Lead
Reproductive and Maternal Health
WHO Country Office – Sierra Leone
Freetown, Sierra Leone

Nilmini HEMACHANDRA
National Professional Officer
WHO Country Office – Sri Lanka
Colombo, Sri Lanka

Chandani Anoma JAYATHILAKA
Medical Officer
Family Health, Gender and Life Course
World Health House
New Delhi, India

Ramez MAHAINI
Coordinator, Maternal and Child Health
Regional Adviser, Reproductive and Maternal Health
WHO Regional Office for the Eastern Mediterranean
Cairo, Egypt

Lamia MAHMOUD
Medical Officer
Maternal and Child Health
WHO Country Office – Pakistan
Islamabad, Pakistan

Léopold OUEDRAOGO
Regional Adviser
Research and Program Development, Reproductive Health
Health Promotion Cluster
WHO Regional Office for Africa
Brazzaville, Republic of Congo

Howard SOBEL
Co-ordinator
Reproductive, Maternal, Newborn, Child and Adolescent Health Division of NCD and Health through Life-Course
Regional Office for the Western Pacific
Manila, Philippines

Claudio SOSA
Regional Advisor, AMRO/CLP
Sexual and Reproductive Health
WHO Regional Office of the Americas
Montevideo, Uruguay

Meera Thapa UPADHYAY
National Professional Officer
WHO Country Office – Nepal
Souleymane ZAN
National Professional Officer,
Making Pregnancy Safer
WHO Country Office – Burkina Faso
Ouagadougou, Burkina Faso
Kathmandu, Nepal

Annex 2. Priority outcomes used in decision-making

Priority outcomes

- Maternal death
- PPH ≥ 1000 ml
- Blood transfusion
- Severe maternal morbidity: intensive care unit admission
- Severe maternal morbidity: shock
- PPH ≥ 500 ml
- Use of additional uterotonics
- Blood loss (ml)
- Postpartum anaemia
- Breastfeeding
- Side-effects
- Maternal well-being
- Maternal satisfaction

Annex 3. Summary and management of declared interests from GDG members

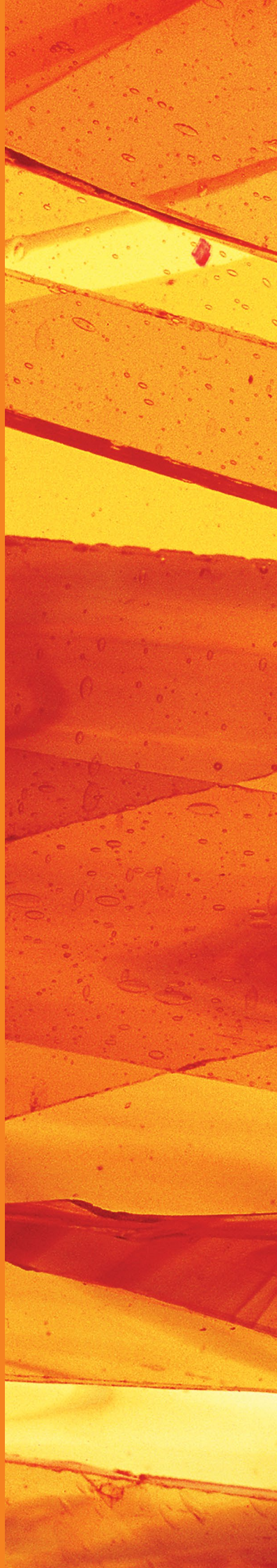
Name	Expertise contributed to guideline development	Declared interest(s)	Management of declared interest(s)
Guideline Development Group (GDG)			
Ireti AKINOLA	Content expert and end-user (obstetrics)	None declared	Not applicable
Shubha ALLARD	Content expert and end-user (haematology)	Barts Health NHS Trust and Queen Mary University of London received a National Institute of Health Research, Health Technology Assessment Programme (NIHR HTA) (UK) for a funded study of cell salvage in caesarean section.	The conflict was not considered serious enough to affect GDG membership or participation
Melania Maria Ramos de AMORIM	Content expert and end-user (obstetrics, evidence synthesis)	None declared	Not applicable
Brendan CARVALHO	Content expert and end-user (anaesthesiology)	None declared	Not applicable
Catherine DENEUX-THARAUX	Content expert (perinatal epidemiology)	None declared	Not applicable
Sue FAWCUS	Content expert and end-user (obstetrics)	None declared	Not applicable
Caroline HOMER	Content expert and end-user (midwifery)	None declared	Not applicable
Simon LEWIN	Content expert (health systems, evidence synthesis and guideline methodology)	Funding for guideline work was received from WHO, the Norwegian Agency for Development Cooperation (NORAD) and the Research Council of Norway to Dr Lewin's research unit.	The conflict was not considered serious enough to affect GDG membership or participation.
Tippawan LIABSUETRAKUL	Content expert and end-user (obstetric epidemiology, evidence synthesis)	None declared	Not applicable
Anita MAEPIOH	Content expert and end-user (nursing)	None declared	Not applicable
Martin MEREMIKWU	Content expert and end-user (neonatology, evidence synthesis)	None declared	Not applicable

Name	Expertise contributed to guideline development	Declared interest(s)	Management of declared interest(s)
Suellen MILLER	Content expert and end-user (midwifery)	Serves as a technical advisor to the Blue Fuzion Group which manufactures and distributes one brand of non-pneumatic anti-shock garment (NASG) – the LifeWrap. The University of California, San Francisco (UCSF) receives a royalty for the trademark name, LifeWrap.	The conflict was not considered serious enough to affect GDG membership or participation.
Rintaro MORI	Content expert and end-user (neonatology, evidence synthesis)	None declared	Not applicable
Ashraf NABHAN	Content expert and end-user (obstetrics)	None declared	Not applicable
Hiromi OBARA	Content expert and implementer (maternal and newborn health)	None declared	Not applicable
Rachel PLACHCINSKI	Women's representative	None declared	Not applicable
Hayfaa WAHABI	Content expert and end-user (public health, obstetrics)	None declared	Not applicable
Dilys WALKER	Content expert and end-user (obstetrics)	Co-founder and President of the NGO PRONTO International. PRONTO designs and implements simulation and team training for obstetric and neonatal emergencies, including postpartum haemorrhage. Professor Walker has donated funds to the organization. PRONTO International has the rights to the low-tech birth simulator, PARTO Pants and the PRONTO Pack simulation training kit.	The conflict was not considered serious enough to affect GDG membership or participation.
Evidence Synthesis Group (ESG)			
Edgardo ABALOS	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Mónica CHAMILLARD	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Virginia DIAZ	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Soo DOWNE	Content expert (evidence synthesis)	None declared	Not applicable

Name	Expertise contributed to guideline development	Declared interest(s)	Management of declared interest(s)
Kenneth FINLAYSON	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Ioannis GALLOS	Content expert (evidence synthesis)	None declared	Not applicable
Leanne JONES	Content expert (evidence synthesis)	None declared	Not applicable
Frances KELLIE	Content expert (evidence synthesis)	None declared	Not applicable
Theresa LAWRIE	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Julia PASQUALE	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable
Myfanwy WILLIAMS	Content expert (evidence synthesis, guideline methodology)	None declared	Not applicable

Web annexes: GRADE Evidence to Decision frameworks and Summary of Findings tables

Web annex	Comparison	Link
1	Oxytocin versus placebo or no treatment	Web annex 1
2	Carbetocin versus placebo or no treatment	Web annex 2
3	Misoprostol versus placebo or no treatment	Web annex 3
4	Ergometrine/methylergometrine versus placebo or no treatment	Web annex 4
5	Oxytocin and ergometrine versus placebo or no treatment	Web annex 5
6	Injectable prostaglandins versus placebo or no treatment	Web annex 6
7	Choice of uterotonic agents	Web annex 7



For more information, please contact:

Department of Reproductive Health and Research
E-mail: reproductivehealth@who.int
www.who.int/reproductivehealth

Maternal, Newborn, Child and Adolescent Health
E-mail: mncah@who.int
www.who.int/maternal_child_adolescent

World Health Organization
Avenue Appia 20, CH-1211 Geneva 27
Switzerland

ISBN 978-92-4-155042-0