WHO recommendation on **Tocolytic therapy for improving preterm birth outcomes**

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Acronyms and abbreviations

BMGF	Bill & Melinda Gates Foundation
CerQUAL	Confidence in the Evidence from Reviews of Qualitative Research
DOI	Declaration of Interest
EtD	Evidence-to-Decision
FIGO	International Federation of Gynecology and Obstetrics
GDG	Guideline Development Group
GSG	Guideline Steering Group
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ICM	International Confederation of Midwives
IM	Intramuscular
MCA	[WHO Department of] Maternal, Newborn, Child and Adolescent Health
MMAT	Mixed Methods Appraisal Tool
NMA	network meta-analysis
PICO	population (P), intervention (I), comparison (C), outcome (O)
RoBANS	Risk of Bias Assessment Tool for Non-randomized Studies
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
SRH	[WHO Department of] Sexual and Reproductive Health and Research
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

Complications of preterm birth are the single largest cause of newborn deaths and deaths among children under the age of five years. Preterm babies who survive are more prone to serious illnesses during childhood. Global efforts to reduce newborn and child morbidity and mortality demand urgent action to address preterm birth.

In 2021, the World Health Organization (WHO) convened the Executive Guideline Steering Group (GSG) for maternal and perinatal health recommendations, which prioritized updating of the WHO recommendations on the use of tocolytic therapy for improving preterm birth outcomes. This decision was based on the availability of new evidence on the efficacy of tocolytic therapy. The recommendation in this document thus supersedes the corresponding tocolytic recommendation in the *WHO recommendations on interventions to improve preterm birth outcomes* published in 2015.

WHAT'S NEW?

In the 2015 guideline, tocolytic treatments (acute and maintenance treatments) were not recommended for women at risk of imminent preterm birth for the purpose of improving newborn outcomes. This recommendation was informed by the lack of substantive benefits of tocolytic treatment, compared with no tocolytic treatment, in terms of reducing adverse perinatal and neonatal outcomes and frequency and severity of side effects.

A review of the evidence in 2022, however, has recommended in favour of nifedipine for acute and maintenance tocolytic therapy for women with a high likelihood of preterm birth, when certain conditions are met. This recommendation was made in light of the updated evidence base that indicates benefits in using this intervention.

Target audience

The primary audiences for this document are health-care professionals responsible for developing national and local health-care protocols and policies, as well as managers of maternal and child health programmes, and policy-makers in all settings. The recommendation will also be useful to those directly providing care to pregnant women and preterm infants, such as obstetricians, paediatricians, midwives, nurses and general practitioners. The information in this document will be useful for developing job aids and tools for pre- and in-service training of health workers to enhance their delivery of maternal and neonatal care relating to preterm birth.

Recommendation development methods

The update of this recommendation was guided by standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development*. The recommendations were developed and updated using the following steps: (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 prioritized questions. The quality of the scientific evidence underpinning the recommendations was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and the GRADE Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. The GRADE evidence-to-decision (EtD) framework – an evidence-to-decision tool that includes 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 assembled for updating this recommendation in March 2022.

Recommendations

The GDG issued one recommendation on tocolytic therapy for improving preterm birth outcomes. To ensure that the recommendation is correctly understood and applied in practice, the GDG provided additional remarks. As the GDG recommended the use of tocolytic therapy in specific contexts, further detail was included about the particular context and which key issues need to be examined. Users of the recommendation should refer to these remarks, which are presented directly beneath the recommendation (section 3.2). The recommendation on the use of tocolytic therapy to improve preterm birth outcomes is given below.

CONTEXT-SPECIFIC RECOMMENDATION

Nifedipine is recommended for acute and maintenance tocolytic therapy for women with a high likelihood of preterm birth for the purpose of improving newborn outcomes, when the following conditions are met:

- Spontaneous preterm labour is suspected or diagnosed
- Gestational age is accurately assessed to be between 24 weeks 0 days and 33 weeks 6 days
- There is no evidence that tocolysis is contraindicated (such as vaginal bleeding, placental abruption or intrauterine infection)
- It permits a single course of antenatal corticosteroids to be administered and/or enables transfer of the mother to a facility where, upon birth, the preterm infant can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including continuous positive airway pressure as needed)
- Adequate birth care is available (including capacity to recognize and safely manage preterm labour and birth)
- Women and families receive adequate information about the benefits and risks of tocolysis, including the lack of information on long-term outcomes.

1 Introduction

1.1 Background

The World Health Organization (WHO) envisions a world where "every pregnant woman and newborn receives quality care throughout pregnancy, childbirth and the postnatal period" *(1)*. High-quality maternal health care for all women and babies is a necessary step towards the achievement of the health targets agreed in the Sustainable Development Goals (SDGs) *(2)* and the targets and indicators of the WHO's Thirteenth General Programme of Work *(3)*, particularly those for achieving universal health coverage.

Ensuring accessibility and acceptability of interventions to improve maternal and newborn health outcomes is consistent with international human rights laws, which include fundamental commitments of states to enable women and adolescent girls to survive pregnancy and childbirth, and to assure their sexual and reproductive health rights and to live a life of dignity. High-quality health care could reduce the profound inequities in maternal and newborn health globally and is essential for improving pregnancy and birth outcomes.

Preterm birth is defined as a baby born prior to 37 completed weeks of gestation *(4)*. Worldwide, an estimated 14.8 million babies are born preterm each year, with most of these babies (81%) being born in Asian and sub-Saharan African countries *(5)*. Preterm birth is the leading cause of death in children under 5 years, and an estimated 35% of neonatal deaths in the first 28 days of life are caused by preterm birth complications *(6, 7)*. Preterm newborns are at increased risk of short-term morbidities, including respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis and sepsis, as well as longer-term morbidities, such as chronic lung disease and neurological disabilities *(8–17)*.

Death and disability following preterm birth can be reduced through interventions provided to the mother before or during pregnancy, and to the preterm newborn after birth. Interventions can be directed at all women to reduce of the risk of preterm birth (i.e. primary prevention), or directed at pregnant women with known risk factors (i.e. secondary prevention). Tertiary prevention interventions are provided to the woman shortly before or during the birth process with the aim of overcoming immediate and future health challenges of the preterm newborn, such as lung immaturity, susceptibility to infection, and neurological complications. Essential and additional care of the preterm newborn to prevent or treat potential complications is also critical to newborn survival without disability. This may include resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support, among others.

Tocolytic drugs (drugs that inhibit contractions of the uterus) can be used to temporarily arrest preterm labour and delay birth. Tocolysis might have an effect on perinatal outcomes by a) allowing more time in-utero for fetal maturation, b) allowing time for administration of antenatal corticosteroids for fetal lung maturation and other newborn health benefits, and/or c) facilitating in-utero transfer of the woman to a higher level of care (for care of the woman, and particularly for the management of the preterm newborn) *(18)*. In recent years, a number of new trials have been published on the effects of different tocolytic agents for women in spontaneous preterm labour.

1.2 Rationale and objectives

Since 2017, the Department of Sexual and Reproductive Health and Research (SRH) at WHO has implemented a "living guidelines" approach to updating maternal and perinatal health recommendations, whereby an Executive Guideline Steering Group (GSG) oversees a systematic prioritization of maternal and perinatal health recommendations in most urgent need of updating *(19)*. Recommendations are prioritized for update based on 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 WHO's recommendation on tocolytic therapy to improve preterm birth outcomes, in response to new, potentially important evidence on this intervention. This decision reflected the large number of randomised trials that have been published since the WHO recommendation on tocolytic therapy was last updated. The primary goal of this update is to improve the quality of care and outcomes for pregnant women and newborns in relation to preterm birth-related care.

This updated recommendation was developed in accordance with the standards and procedures in the *WHO handbook for guideline development*, including the synthesis of available research evidence, use of the Grading of Recommendations Assessment,

Development and Evaluation (GRADE) methodology[1], and formulation of recommendations by a Guideline Development Group (GDG) composed of international experts and stakeholders. The recommendation in this document thus supersedes the recommendation on tocolytics that was published as part of the WHO recommendations on interventions for improving preterm birth outcomes in 2015.

1.3 Aim

The primary aim of this recommendation is to improve outcomes among women at risk of preterm birth and babies born preterm. Tocolytic agents have the potential to delay birth, as well as impact health outcomes for the woman and her baby. This recommendation thus provides a foundation for sustainable implementation of tocolytic therapy as one of the interventions for improving preterm birth outcomes.

1.4 Target audience

This recommendation is primarily for health-care professionals who are responsible for developing national and local health guidelines and protocols (particularly those related to management of preterm birth) and those involved in the provision of care to women during labour and childbirth, including midwives, nurses, general medical practitioners, obstetricians, managers of maternal and child health programmes and relevant staff in ministries of health and training institutions, in all settings.

This recommendation will also be of interest to women giving birth in a range of resource settings, as well as professional societies involved in the care of pregnant women, nongovernmental organizations concerned with promoting people-centred maternal care and implementers of maternal and perinatal health programmes.

1.5 Identification of priority questions and outcomes

The priority question and sub-questions for updating this recommendation were identified by the WHO Executive Guideline Steering Group through a systematic prioritization process in the first quarter of 2021. The recommendation on tocolytics was prioritized for updating primarily on the basis of new, potentially important evidence affecting this recommendation.

The priority outcomes were aligned with the prioritized outcomes from the 2015 *WHO recommendations on interventions to improve preterm birth outcomes.* These outcomes were initially identified through consultation with international stakeholders (including midwives, obstetricians, neonatologists, researchers, experts in health programmes and representatives of user groups) and a prioritization of outcomes by the 2015 guideline panel. Two additional outcomes were included (maternal well-being and maternal satisfaction) for this update to ensure that evidence synthesis and recommendation decision-making by the GDG are driven by outcomes that are important to women, and that the final recommendation is women-centred. All the outcomes were included in the scope of this document for evidence searching, retrieval, synthesis, grading and formulation of the recommendation. The list of priority outcomes is provided in Annex 2.

1.6 Scope of the recommendation

This recommendation focuses on the use of tocolytic therapy among women with a high likelihood of preterm birth, the effectiveness and safety of specific tocolytic agents (acute or maintenance therapy), and the populations of women for whom tocolytic therapy should or should not be used.

The priority question that guided evidence synthesis and decision-making for this recommendation is presented below using the Population (P), Intervention (I), Comparison (C), Outcome (O) (PICO) format. The sub-questions are also listed below.

PRIORITY QUESTION AND SUB-QUESTIONS

For women at risk of imminent preterm birth (P), is the use of tocolytic agent(s) (I) compared with placebo or no tocolytic (C) effective in delaying preterm birth and reducing adverse neonatal outcomes (O)?

- If so, which tocolytic should be used considering comparative efficacy and safety?
- Which population of women should or should not be offered tocolytics?
- Should a maintenance regimen be used?

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

2 Methods

The recommendation was developed using the standardized operating procedures in accordance with the process described in the *WHO handbook for guideline development (20)*. 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 recommendation; and (v) planning for the dissemination, implementation, impact evaluation and updating of the recommendation.

In 2021, updating the WHO recommendation on tocolytic therapy was identified by the Executive GSG as a high priority in response to new evidence on the benefits and possible harms of this intervention. Six main groups participated in this process. Their specific roles are described below.

2.1 Executive Guideline Steering Group

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. Members of the Executive GSG serve for a period of three years and advise WHO on the prioritization of new and existing questions in maternal and perinatal health for the development or updating of recommendations *(19)*.

2.2 WHO Steering Group

The WHO Steering Group, comprising WHO staff members from the Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health managed the updating process. The WHO Steering Group drafted the key recommendation questions in PICO format, identified the systematic review teams and guideline methodologists, as well as members of the Guideline Development Group and the External Review Group. In addition, the WHO Steering Group supervised the retrieval and syntheses of evidence, organized the Guideline Development Group meetings, finalized the recommendation document, and managed 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 recommendations, 18 external experts and relevant stakeholders were invited to participate as members of the Guideline Development Group (GDG). These individuals were drawn from a pool of approximately 50 experts and relevant stakeholders that constitute the WHO Maternal and Perinatal Health Guideline Development Group. Those selected were a diverse group with expertise in research, guideline development methods, and clinical policy and programmes relating to improving preterm birth outcomes, as well as a representative of the affected population.

The GDG members were selected in a way that ensured geographic representation and gender balance and that there were no important conflicts of interest. Based on the documents prepared by the Steering Group, the GDG appraised and interpreted the evidence, and formulated the final recommendations at meetings convened on 27 January–1 February 2022 and 1–3 March 2022. The group also reviewed and approved the final recommendation document. The members of this group are listed in Annex 1.

2.4 Evidence Synthesis Group

WHO convened an Evidence Synthesis Group (ESG) composed of guideline methodologists and systematic review teams for the conduct or updating of systematic reviews, appraisal of evidence, and development of the evidence-to-decision frameworks.

Technical experts from the Burnet Institute, Australia, and the Cochrane Pregnancy and Childbirth Group (CPC), United Kingdom, served as the guideline methodologists. In relation to quantitative evidence on the effects of the interventions, the Cochrane 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 coordinated with the review authors on the conduct of a systematic review and network meta-analysis (NMA) on tocolytic therapy. The guideline methodologists appraised the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(21)*.

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. This included:

- a systematic review of qualitative, quantitative and mixed-methods studies related to women's and health-care professionals' views and experiences of tocolytic therapy
- a systematic review of studies on cost–effectiveness of tocolytic therapy.

The Steering Group worked closely with the Evidence Synthesis Group to review the evidence and prepare the GRADE EtD frameworks. Members of the Evidence Synthesis Group attended the GDG meetings to provide an overview of the synthesised evidence, and to respond to technical queries from the GDG. The members of the Evidence Synthesis Group are listed in Annex 1.

2.5 External partners and observers

Representatives of the United States Agency for International Development (USAID), the Bill & Melinda Gates Foundation (BMGF), the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) and the International Pediatric Association (IPA) participated in the GDG meeting as observers. These organizations with their long history of collaboration with the relevant WHO Departments in guideline dissemination and implementation, were identified as significant implementers of the recommendations. The list of observers who participated in the GDG meeting is included in Annex 1.

2.6 External Review Group

The recommendation was reviewed by an external review group composed of five technical experts with interest and expertise in the provision of evidence-based care to improve outcomes after preterm birth. The group was gender balanced and members were from four different WHO regions (African Region, Region of the Americas, South-East Asia Region and Western Pacific Region). 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 External Review Group are listed in Annex 1.

2.7 Evidence identification and retrieval

Evidence to support the update of the recommendation was derived from several sources by the systematic review teams working in collaboration with the WHO Steering Group.

2.7.1 Evidence on effectiveness

To inform the development of the recommendations, a new systematic review and network meta-analysis on the comparative efficacy and safety of different classes of tocolytics (betamimetics, cyclo-oxygenase inhibitors, calcium channel blockers, magnesium sulfate, nitric oxide donors, and combinations of tocolytics) against placebo or each other was commissioned *(22)*. An external group of systematic reviewers was asked to prepare a review protocol with a clear PICO question and criteria for identification of studies, including search strategies for different bibliographic databases, methods for assessing risk of bias and a data analysis plan. The WHO Steering Group and selected members of the evidence synthesis group then reviewed and endorsed the protocol before the systematic review was conducted.

The search strategies employed to identify the studies and the specific criteria for inclusion and exclusion of studies were described in the systematic review *(22)*. In brief, studies were identified from searches of the Cochrane Pregnancy and Childbirth Group's Trials Register. This Register is maintained by the Trials 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. Studies from low-, middle- and high-income countries were considered and there were no language restrictions. The entire systematic review development process was iterative, with the systematic reviewers and methodologists constantly communicating with the WHO Steering Group to discuss challenges and agree on solutions.

In addition, a systematic review update was commissioned to examine the efficacy and safety of tocolytics among specific groups of women to respond to priority questions that could not be addressed by the network meta-analysis. The authors of an existing systematic review of non-randomized studies that informed the previous recommendation were requested to update this review *(23)* within a specified time period in consultation with the WHO Steering Group.

2.7.2 Evidence on values, resource use and cost–effectiveness, equity, acceptability and feasibility

Values, equity, acceptability and feasibility

A systematic review was conducted on factors influencing appropriate use of interventions for management of women experiencing preterm birth *(24)*. This review was the primary source of evidence on acceptability, feasibility and equity. This review included primary qualitative, quantitative, and

mixed-methods studies that discussed use of tocolytic therapy to suppress preterm birth. An iterative narrative synthesis approach to analysis was taken.

Resource use and cost–effectiveness

Evidence on resource use and cost–effectiveness was based on a systematic review of the literature *(25)*. The review aimed to synthesize all available evidence on the cost–effectiveness of tocolytic therapy for improving preterm birth outcomes. Eligible studies were identified from specialist health economic databases (NHS Economic Evaluation Database and EconLit) and medical databases (PubMed, Embase, CINAHL and PsycInfo). Eligible studies were full economic evaluations that assessed cost–benefit, cost–effectiveness and/or cost–utility for women who received tocolytic therapy. Two reviewers independently screened citations, extracted data and assessed study quality.

2.8 Quality assessment and grading of the evidence

2.8.1 Quality assessment of primary studies included in the reviews

All studies meeting the inclusion criteria for the Cochrane review were evaluated by two review authors against predefined criteria to select studies that, based on available information, were deemed to be sufficiently trustworthy to be included in the analysis. These criteria were developed by Cochrane Pregnancy and Childbirth and include issues related to research governance, baseline characteristics of participants, feasibility of the included population and plausibility of results.

The assessment of the quality of individual studies included in the Cochrane review 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 *(26)*. Each included study was assessed and rated by reviewers to be at low, high or unclear risk of bias for random sequence generation and allocation concealment (selection bias), blinding of study personnel (performance bias) and participants (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias, such as publication bias. The assessment along these domains provided an overall risk of bias for each included study, which indicates the likely magnitude and direction of the bias and how it is likely to affect the review findings. Overall, around 14 per cent of studies were assessed as at low risk of bias, 84 per cent at unclear risk and 2 per cent at high risk.

Other systematic reviews that included randomized trials also used the process outlined above. For non-randomized quantitative studies, assessment of study quality was in accordance with Cochrane handbook guidance, using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) or Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) *(27)*.

Studies identified in the mixed-methods systematic review into women's and health-care professionals' views and experiences of tocolytic therapy were assessed using an adapted Mixed Methods Appraisal Tool (MMAT) *(24)*. MMAT is a critical appraisal tool designed specifically for mixed methods reviews and includes assessment of different criteria for different study designs (quantitative, qualitative and mixed-methods).

The quality of included studies on cost–effectiveness was assessed using the International Society of Pharmacoeconomics and Outcomes Research Taskforce Consolidated Health Economic Evaluation Reporting Standards statement *(28)*.

2.8.2 Assessment of certainty of the effectiveness evidence

The GRADE working group's approach for rating the certainty in network meta-analysis was used for rating the quality of effect estimates for the comparisons of interest *(29, 30)*. The appraisal of certainty for direct, indirect, and network evidence was performed sequentially in the following order. First, the quality of direct evidence (where available) for a given outcome was rated using the standard GRADE approach based on consideration of study design limitations (risk of bias), inconsistency (heterogeneity or variability in results), indirectness (differences in study populations), imprecision (small study populations and few events) and publication bias *(26)*. Then the certainty of the indirect evidence for the same outcome was determined based on the lower of quality ratings of 'first-order' loop in the network diagram for this outcome. The final step was the determination of the certainty of network evidence based on: (i) the higher of 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).

Summary of findings tables were prepared that included the effect estimate and quality judgements for each outcome from direct evidence, as well as

the effect estimates from indirect evidence and the NMA, and an overall judgement of quality for each outcome based on the network estimate. Summary of findings tables were prepared for all comparisons (each tocolytic versus placebo or no tocolytic).

A separate systematic review on the use of tocolytic therapies in special populations also used the GRADE approach process (outlined above) to assess the quality of randomized trials. For non-randomized quantitative studies, assessment of study quality was in accordance with Cochrane handbook guidance, using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) *(27)*.

GRADE certainty of the evidence

The certainty of evidence for each outcome was rated as 'high', 'moderate', 'low' or 'very low' as defined by the GRADE methodology:

- **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; and
- **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

2.8.3 Assessment of the certainty (confidence) of the qualitative evidence

The findings of qualitative studies included in the mixed-methods systematic review were appraised using the GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) tool *(24)*. 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 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.

2.9 Formulation of the recommendation

The WHO Steering Group supervised the preparation and finalization of summary of findings tables and narrative evidence summaries in collaboration with the Evidence Synthesis Group using the GRADE EtD framework *(31)*. The EtD framework includes explicit and systematic consideration of evidence on the intervention in terms of specified domains: effects, values, resources, equity, acceptability and feasibility. Using the EtD framework template, the Steering Group and Evidence Synthesis Group created summary documents for each priority question covering evidence on each domain. 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.

The WHO Steering Group provided the EtD framework, including evidence summaries and summary of findings tables, to GDG members two weeks prior to the GDG meeting. The GDG members were asked to review and electronically provide comments on the documents before the GDG meetings. During the online meetings of the GDG, under the leadership of the GDG chairperson, the GDG members collectively reviewed the framework and any comments received.

The purpose of the meetings was to formulate recommendations, reach consensus on any recommendations and, where required, provide the specific context for recommendations, based on explicit consideration of the range of evidence presented in the EtD framework and the judgement of the GDG members.

In formulating this recommendation, the GDG considered the effectiveness of a tocolytic agent compared to placebo for each outcome and across multiple outcomes and the certainty of the evidence for each tocolytic agent. The Surface under the cumulative ranking curve (SUCRA) – a numeric presentation of overall ranking – was considered by the GDG. However, SUCRA alone does not reflect the certainty of the evidence; the absolute effect on a given outcome; or the impact of other factors (such as cost, acceptability, feasibility). Also, differences in SUCRA may be minimal, or may be explained by chance.

In addition to considering evidence on the effectiveness of the intervention, the GDG applied the recommended GRADE evidence-to-decision framework and considered separately synthesized evidence on values (outcome importance) of the stakeholders; resource use and cost–effectiveness of the intervention; acceptability and feasibility of the intervention; and the impact of the intervention on equity. For each of these domains, an appraisal of the certainty of evidence was performed using appropriate methods including GRADE or GRADE CerQual depending on the type of synthesis. As this process produced a certainty of evidence rating for

multiple domains (in addition to certainty of evidence on the effectiveness of the intervention), it was the view of the GDG that a single overall 'certainty' rating should not be assigned to the recommendation. In addition, providing the certainty of evidence for effectiveness alone within the recommendation itself would not adequately reflect the consideration of certainty for all types of evidence, and could potentially confuse the target audience.

The GDG classified the 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. 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.

This classification approach has been used for the development of all consolidated WHO maternal and perinatal health guidelines and updates of recommendations since 2016, spanning more than 90 individual recommendations. The approach was adopted in response to the feedback received from end users of maternal and perinatal health guidelines about the challenges of interpreting recommendations coupled with specific evidence ratings. The GRADE Public Health Group has acknowledged that a key challenge for GRADE in public health is to identify how to reconcile the tension between the methodologically correct presentation of recommendations and the implications of strong versus conditional recommendations from the perspective of decision-makers *(32)*.

2.10 Management of declaration of interests

WHO has a robust process to protect the integrity of its normative work, as well as to protect the integrity of the individual experts with whom it collaborates. WHO requires that experts serving in an advisory role disclose any circumstances that could give rise to actual or ostensible conflict of interest. The disclosure and the appropriate management of relevant financial and non-financial conflicts of interest of GDG members and other external experts and contributors are 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 according to the guidelines for declaration of interest (DOI) for WHO experts *(20)*. All GDG members were therefore required to complete a standard WHO DOI form before engaging in the guideline development process and before participating in guideline-related processes. A short biography of the GDG members was also published on WHO's SRH 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 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 guideline and recommendation development process. To ensure consistency, the WHO 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. All findings from the DOI statements received were managed in accordance with the WHO procedures to ensure that the work of WHO and the contribution of its experts is, actually and ostensibly, objective and independent. Where conflicts of interest were not considered significant enough to pose any risk to the guideline development process or to reduce its credibility, experts were only required to openly declare such conflicts 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.

2.11 Decision-making during the GDG meetings

The GDG meetings were designed to allow participants to discuss the supporting evidence and to reach a consensus on the final wording of each recommendation. 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. No GDG member expressed opposition to the recommendation. Where required, the GDG determined the context of the recommendation 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.

2.12 Document preparation and peer review

The WHO Steering Group made a draft version of the EtD framework available to the participants two weeks before the meeting for their comments. During the meeting, the framework was modified in line with the participants' deliberations and remarks. Following the meeting, the WHO Steering Group worked with the guideline methodologists to prepare a full recommendation document to accurately reflect the deliberations and decisions of the participants. The draft document was sent electronically to GDG members for their final review and approval. The final document was also sent for peer review to five external independent experts who were not involved in the recommendation development. The WHO Steering Group evaluated the inputs of the peer-reviewers for inclusion in this document. After the meetings and external peer reviews, the modifications made by the WHO Steering Group to the document consisted only of the correction of factual errors and edits to address any lack of clarity.

3 Recommendation and supporting evidence

The GDG issued one main recommendation on tocolytic therapy which consolidates their interpretation of the evidence for the key priority question and sub-questions. This section outlines the recommendation corresponding to the priority question in section 1.6. To ensure that the recommendation is correctly understood and appropriately implemented in practice, additional 'remarks' reflecting the summary of the discussions by the GDG are included under the recommendation. The recommendation should be applied in conjunction with the implementation considerations.

The summary of findings tables and EtD framework — presenting the balance between the desirable and undesirable effects, values of stakeholders, resource requirements, cost–effectiveness, acceptability, feasibility and equity that were considered in formulating each recommendation — are presented separately in a Web Annex (https://apps.who.int/iris/bitstream/handle/10665/363130/9789240057241-eng.pdf) to this document.

3.1 Recommendation

CONTEXT-SPECIFIC RECOMMENDATION

Nifedipine is recommended for acute and maintenance tocolytic therapy for women with a high likelihood of preterm birth for the purpose of improving newborn outcomes, when the following conditions are met:

- Spontaneous preterm labour is suspected or diagnosed
- Gestational age is accurately assessed to be between 24 weeks 0 days and 33 weeks 6 days
- There is no evidence that tocolysis is contraindicated (such as vaginal bleeding, placental abruption or intrauterine infection)
- It permits a single course of antenatal corticosteroids to be administered and/or enables transfer of the mother to a facility where, upon birth, the preterm infant can receive adequate care (including resuscitation, kangaroo mother care, thermal care, feeding support, infection treatment and respiratory support including continuous positive airway pressure as needed)
- Adequate birth care is available (including capacity to recognize and safely manage preterm labour and birth)
- Women and families receive adequate information about the benefits and risks of tocolysis, including the lack of information on long-term outcomes.

REMARKS

- The GDG considered nifedipine to be the preferred option as the balance of benefits and harms, cost, acceptability and feasibility was superior to other tocolytic agents. The GDG acknowledged that oxytocin receptor antagonists and nitric oxide donors can prolong pregnancy, but are not available in many countries and can be more costly.
- Based on the available trials, the commonly-used regimen for nifedipine (immediate-release) is an initial oral dose of 20 mg followed by 10 mg every 6 hours for 3–7 days or until transfer is completed, whichever comes first.
- The GDG noted that COX inhibitors do have a tocolytic effect (delaying birth up to 48 hours) and may be considered in the management of preterm labour prior to 28 weeks . They are contraindicated, however, in the third trimester due to an association with increased risk of premature closure of the ductus arteriosus and the potential for renal dysfunction leading to oligohydramnios.
- Available trials suggest that while magnesium sulfate has a tocolytic effect (delaying birth by 48 hours), other tocolytic agents have greater benefits and fewer side-effects.
- Although betamimetics appear effective in delaying birth, their use is associated with a risk of serious maternal adverse effects, which may sometimes be life-threatening.
- Combination therapy does not have more benefits than monotherapy options, and therefore the GDG recommends monotherapy only.
- The GDG noted that 40% of tocolytic trials used an acute plus maintenance regimen, though the benefits of a maintenance regimen (beyond acute tocolysis) could not be determined. The GDG therefore agreed that acute plus maintenance tocolysis with nifedipine is optimal in the management of preterm labour, though further research is required.

REMARKS *(continued)*

- The GDG acknowledged that trials largely enrolled women with intact membranes – only 9% of women in these trials had ruptured membranes. There was insufficient evidence to conclude on the benefits or possible harms of tocolysis in this subgroup. The GDG therefore indicated that tocolytics can be considered in women with ruptured membranes, if there are no contraindications such as intrauterine infection. This was considered a research priority.
- The available trials included women with singleton and multiple pregnancies. While it was not possible to draw conclusions on the effects of tocolytics in women with multiple pregnancies, they are likely to benefit from tocolysis.
- Women and families should receive adequate information about the benefits and risks of tocolysis. There is a lack of information on the long-term outcomes following tocolysis, which should be discussed with the woman and her family in order for an informed decision regarding the woman's care to be taken.
- There are separate WHO recommendations relating to use of antenatal corticosteroids for women with a high likelihood of preterm birth prior to 34 weeks' gestation *(33)*.

4 Dissemination and implementation of the recommendation

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

4.1 Dissemination and evaluation

An executive summary containing the recommendation, remarks, implementation considerations and research priorities will be prepared for public dissemination.

The WHO steering group will also develop tools to aid understanding and adaptation of the recommendation to local contexts, including an evidence brief on use of tocolytic therapy and a clinical algorithm. The recommendation and 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 recommendation will be published on the WHO's SRH website, and highlighted as part of the monthly *HRP News*. This newsletter currently reaches over 8000 subscribers including clinicians, programme managers, policy-makers and health service users from 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 recommendation from this publication will be translated into the six UN languages for dissemination through the WHO regional and country offices and during meetings organized by, or attended by, staff of the WHO SRH and MCA Departments. Technical assistance will be provided to any WHO regional office willing to translate the full recommendation into any of these languages.

In addition, the publication of journal articles presenting the recommendation and key implementation considerations will be considered, in compliance with WHO's open access and copyright policies. Relevant WHO clusters, departments and partnerships, such as the Partnership for Maternal, Newborn and Child Health (PMNCH), will also be part of this dissemination process.

In order to ensure this recommendation has impact on maternal and perinatal health at country level, co-ordinated action between international agencies, national departments of health and key maternal and perinatal health stakeholders is required. National and sub-national working groups should assess current national guidelines and protocols, and determine whether development of new guidelines or updating is required in line with this new WHO recommendation. WHO staff at Headquarters, Regional and Country level, as well as international agency partners and international professional societies (such as FIGO and ICM, as well as national professional associations) can support national stakeholders in developing or revising existing national guidelines or protocols, and optimizing their implementation.

In the context of humanitarian emergencies, the adaptation of the current recommendation should consider the integration and alignment with other response strategies. Additional considerations to the unique needs of women in emergency settings, including their values and preferences, should be made. Context-specific tools and toolkits may be required in addition to standard tools to support the implementation of the recommendation in humanitarian emergencies by stakeholders.

4.2 Implementation considerations

The successful introduction of evidence-based policies related to the use of tocolytic therapy to improve preterm birth outcomes into national programmes and health services depends on well-planned and participatory, consensus-driven processes of adaptation and implementation. These processes may include developing or revising existing national guidelines and/or clinical protocols based on this document. The recommendation in this document should be adapted into local appropriate documents that are able to meet the specific needs of each country and health services. Modifications to the recommendation, if necessary, should be limited to conditional recommendations, and justifications for any change should be made in an explicit and transparent manner. The Department of Sexual and Reproductive Health and Research and the Department of Maternal, Newborn, Child and Adolescent Health at WHO will support national and subnational subgroups to adapt and implement the recommendation based on existing strategies.

Implementation of tocolytic therapy needs to be made appropriate to local needs, intended users and recipients, and local health systems. As part of the recommendation development process, overarching implementation considerations were developed, which may help to assist policy-makers and clinicians to better prepare for implementation.

Considerations for implementation of tocolytic therapy are outlined in Table 1.

Table 1: Overarching implementation considerations for tocolytic therapy

Implementation consideration	Description
Accurate assessment of gestational age	This includes a need to ensure that health-care professionals are aware of the importance of ultrasound dating in the management of preterm birth, ensuring that early pregnancy ultrasound is routinely practiced, optimising the coverage of sonographers or other health-care professionals skilled in ultrasound dating, and ensuring that ultrasound equipment is available at the health facility or in antenatal care. Standards, guidelines and training curricula in relation to gestational age estimation would also be required *(34)*.
Shared decision-making, counselling, and family engagement	This includes that resources are in place to support shared decision-making between the woman, her family, and health-care professionals about the potential short- and long-term consequences of tocolytic therapy and preterm birth, decisions about resuscitation, limits of viability, benefits and harms of acute and maintenance therapies, and long-term outcomes. This also includes that women, partners, and families receive education and educational materials on signs of preterm birth and preterm labour management, along with sufficient time and opportunity to discuss preterm birth management plans with health-care professionals. At the time of administration, discussion and consideration of whether women have a preference for a tocolytic option may be appropriate.
Appropriate settings for administration	Appropriate settings for administration of tocolytic therapy include settings where 1) diagnosis of imminent preterm birth at correct gestational age can be made reliably, 2) maternal infection can reliably be excluded, 3) availability of adequate childbirth and preterm newborn care environments (including resuscitation, kangaroo mother care, feeding support, infection treatment, respiratory support, and safe oxygen use), and 4) whether improvements to referral systems are needed, including transportation. Furthermore, among women who have received tocolytic therapy and who then have preterm labour slow or abate, defining appropriate discharge criteria and subsequent follow-up to ensure safety is required.
Procurement and administration	This includes that there is sufficient funding and budget allocation to ensure procurement and distribution of tocolytics and prevent stock-outs; that tocolytics are readily available in the antenatal, labour and emergency obstetric wards; that the safe administration of tocolytics can be simplified for health-care professionals, and that there is standardized communication about administration and dosing during handover and referral.
Guideline and clinical protocol adaptation	This includes ensuring that there has been a multi-stakeholder, consensus-driven process for local guideline adaptation and implementation; that guidelines and clinical protocols are consistent between WHO, national, sub-national and facility-levels, and that national guidelines have clear criteria on appropriate use and acceptable regimens for tocolytics.
Strategies to improve tocolytic use	Prior to implementation, understanding that there are potential barriers to use of tocolytics is important, including that health-care professionals are aware of the benefits of tocolysis, and whether health-care professionals have any scepticism or concerns about adverse effects of tocolysis that can be addressed. Specific strategies that may improve appropriate use include: - Training for health-care professionals on safe and appropriate use of tocolytics - Reminder systems, educational materials, and decision aids available and accessible for health-care professionals - Key performance indicators and audit and feedback available and accessible for tocolytics - Appointing change champions or opinion leaders to promote appropriate use of tocolytics.

4.3 Anticipated impact on the organization of care and resources

Effective implementation of the recommendation in this guideline may require re-organization of care and redistribution of health-care resources, particularly in low- and middle-income countries. The potential barriers to implementation include:

- Non-availability or irregular supply of essential medicines (e.g. tocolytic drugs such as oral nifedipine, or other medicines used in preterm labour management such as antibiotics, corticosteroids, magnesium sulfate,) and lack of equipment and supplies that are often used for preterm babies (such as oxygen, resuscitator, masks, nasal prongs, continuous positive airway pressure [CPAP] machines, pulse oximeter, incubators, and radiant warmers);
- Lack of human resources with the necessary expertise and skills to implement the recommended practices and monitor the clinical response of the newborn (e.g. application of continuous positive airway pressure, intubation, oxygen therapy);
- Low certainty of gestational age estimation, particularly for pregnant women living in settings where antenatal ultrasound is not routinely available;
- Lack of effective referral mechanisms and care pathways that ensure management of women with preterm labour and preterm newborns within a continuum.

To overcome these barriers, the Guideline Development Group (GDG) noted that the following issues should be considered before the recommendation made in this guideline is applied:

- Local protocols should be developed that integrate the management of women at risk of imminent preterm birth and preterm newborns within a continuum, with due consideration for contextual factors that influence preterm newborn survival.
- Careful attention should be paid to dating of pregnancy with the best method available during early antenatal care visits.
- Health-care staff should be trained on how to determine the best estimate of gestational age and clinical features of women in spontaneous preterm labour.
- Local arrangements should be made to ensure ample and consistent supplies of tocolytic drugs.
- Consideration should be given to all other aspects of maternal and newborn care quality at the health-care facility level, including the provision of radiant warmers and kangaroo mother care for preterm newborns.
- Clear referral pathways for women at risk of imminent preterm birth should be established within the health-care facility.

4.4 Monitoring and evaluating guideline implementation

The implementation and impact of this recommendation will be monitored at the health-service, regional and country levels, based on clearly defined criteria and indicators that are associated with locally agreed targets. In the 2015 *WHO recommendations on interventions to improve preterm birth outcomes*, the GDG suggested a set of outcomes, measures and indicators that can be adapted at regional and country levels to assess the impact of guideline implementation and adherence to the guideline recommendations. In collaboration with the monitoring and evaluation teams of the WHO Department of Maternal, Newborn, Child and Adolescent Health and the Department of Sexual and Reproductive Health and Research, data on country- and regional-level implementation of the recommendation will be collected and evaluated in the short to medium term to evaluate its impact on the national policies of individual WHO Member States.

Interrupted time series, clinical audits or criterion-based clinical audits could be used to obtain relevant data related to tocolytic therapy. Clearly defined review criteria and indicators are needed and these could be associated with locally agreed targets. In this context, the following indicators could be considered.

INDICATOR	NUMERATOR	DENOMINATOR
Coverage	All eligible women who gave birth between 24 and 34 weeks of gestational age and received a tocolytic	All eligible women who gave birth between 24 and 34 weeks of gestational age

5 Research implications

The GDG identified important knowledge gaps directly related to the PICO question, or which may have a direct impact on the implementation of this recommendation. The following questions were identified as high priority:

- What are the effects of tocolytic therapy on substantive newborn outcomes (including severe morbidity and mortality outcomes)?
- What are the long-term outcomes of women and babies exposed to tocolytic therapy?
- What are the benefits and possible harms of acute plus maintenance tocolytic therapy[2] compared to acute tocolysis alone?
- Are there infection-related harms associated with the use of tocolytic therapy in women with preterm prelabour rupture of membranes?
- What are the main outcomes that women (and their families) value in relation to the use of tocolytic therapy for improving preterm newborn outcomes?
- What factors (barriers/facilitators) affect the appropriate use and potential scale-up of tocolytic therapy in limited-resource settings, and how can these factors be addressed through implementation research?
- How can implementation and scale up of tocolytic therapy be optimised to ensure equitable distribution of benefits, including for groups experiencing disadvantage (such as racial, ethnic, or minority populations)?
- What is the cost–effectiveness of calcium channel blockers (nifedipine) in the management of women in preterm labour?
- How can shared decision-making about the use of tocolytics with women experiencing preterm birth be most effectively supported?

[2] Maintenance therapy is defined as the use of a tocolytic after the first 48 hours with the same tocolytic or an alternative tocolytic.

6 Updating the recommendation

The Executive 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. This recommendation will be included in those reviews. In the event that new evidence is identified that could potentially impact the current evidence base, this recommendation may be updated. If no new reports or information is identified, the recommendation may be revalidated.

Following publication and dissemination of the updated recommendation, any concerns about the validity of the recommendation should be promptly communicated to the guideline implementers.

WHO welcomes suggestions regarding additional questions for inclusion in recommendations. Please email your suggestions to srhmph@who.int.

7 References

1. 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.
2. Sustainable Development Goals. United Nations; 2022. (https://sdgs.un.org/goals, accesssed 1 July 2022).
3. Thirteenth general programme of work, 2019–2023. Geneva: World Health Organization; 2018.
4. ICD-11 for Mortality and Morbidity Statistics (version 02/2022). (https://icd.who.int/browse11/l-m/en accessed 20 September 2022)
5. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):e37–e46.
6. Wardlaw T, You D, Hug L, Amouzou A, Newby H. UNICEF Report: enormous progress in child survival but greater focus on newborns urgently needed. Reprod Health. 2014;11:82.
7. Yadav S, Lee B, Kamity R. Neonatal respiratory distress syndrome. Treasure Island (FL): StatPearls Publishing; 2021.
8. Patel RM. Short- and long-term outcomes for extremely preterm infants. Am J Perinatol. 2016;33(3):318–28.
9. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the short- and long-term respiratory outcomes of prematurity and bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2015;192(2):134–56.
10. Schnabl KL, Van Aerde JE, Thomson AB, Clandinin MT. Necrotizing enterocolitis: a multifactorial disease with no cure. World J Gastroenterol. 2008;14(14):2142–61.
11. Wallenstein MB, Bhutani VK. Jaundice and kernicterus in the moderately preterm infant. Clin Perinatol. 2013;40(4):679–88.
12. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379(9814):445–52.
13. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261–9.
14. Platt MJ. Outcomes in preterm infants. Public Health. 2014;128(5):399–403.
15. Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet. 2013;381(9862):223–34.
16. van Dommelen P, Verkerk PH, van Straaten HL, Dutch Neonatal Intensive Care Unit Neonatal Hearing Screening Working Group. Hearing loss by week of gestation and birth weight in very preterm neonates. J Pediatr. 2015;166(4):840–3 e1.
17. O'Connor AR, Wilson CM, Fielder AR. Ophthalmological problems associated with preterm birth. Eye. 2007;21(10):1254–60.
18. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev. 2014(2):CD004352.
19. Vogel JP, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health. BMJ Glob Health. 2019;4(4):e001683.
20. WHO Handbook for Guideline Development (second edition). Geneva: World Health Organization; 2014.
21. 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.
22. Wilson A, Hodgetts-Morton VA, Marson E, Markland A, Larkai E, Papadopoulou A, et al. Tocolytics for delaying preterm birth: a network meta-analysis. Cochrane Database 2021, (4), [CD014978]. (https://doi.org/10.1002/14651858.CD014978, accessed 1 July 2022).
23. Yamaji N, Suzuki H, Saito K, Swa T, Namba F, Vogel JP, et al. The use of tocolysis in women at <28 weeks' gestation, multiple pregnancies and a growth-restricted fetus: a systematic review. Under review.

24. Zahroh RI, Hazfiarini A, Eddy KE, Vogel JP, Tunçalp Ö, Minckas N, Althabe F, Oladapo OT, Bohren MA. Factors influencing appropriate use of interventions for management of women experiencing preterm birth: A mixed-methods systematic review and narrative synthesis. PLoS Med. 2022 Aug 23;19(8):e1004074. doi: 10.1371/journal.pmed.1004074. PMID: 35998205; PMCID: PMC9398034.

25. Sebastian E, Bykersma C, Egglestone A, Eddy KE, Chim ST, Zahroh RI, et al. Cost-effectiveness of antenatal corticosteroids and tocolytics in the management of preterm birth: a systematic review. eClinicalMedicin. 2022;49:101496. (doi: 10.1016/j.eclinm.2022.101496, accessed 1 July 2022).

26. Schünemann H, Brożek J, Guyatt G, Oxman A., editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. GRADE Working Group; 2013. (https://gdt.gradepro.org/app/handbook/handbook.html, accessed 1 July 2022).

27. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2. 2021.

28. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013;346:f1049.

29. 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.

30. 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.

31. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. Marcos GRADE de la evidencia a la decisión (EtD): un enfoque sistemático y transparente para tomar decisiones sanitarias bien informadas. 1: Introducción [GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction]. Gac Sanit. 2018;32(2):166.e1–166.e10 (doi: 10.1016/j.gaceta.2017.02.010 accessed 1 July 2022).

32. Hilton Boon M, Thomson H, Shaw B, Akl EA, Lhachimi SK, Lopez-Alcalde J, et al. Challenges in applying the GRADE approach in public health guidelines and systematic reviews: a concept article from the GRADE Public Health Group. J Clin Epidemiol. 2021;135:42–53.

33. WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. Geneva: World Health Organization; 2022.

34. WHO recommendations on antenatal care for a positive pregnancy experience: ultrasound examination. Highlights and key messages from the World Health Organization's 2016 global recommendations. Geneva: World Health Organization; 2018.

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Annex 2. Priority outcomes used in decision-making

Priority outcomes

Critical maternal outcomes considered were:

- Severe maternal morbidity or death (e.g. maternal admission to intensive care unit or other markers of severe maternal illness);
- Maternal infectious morbidity (i.e. chorioamnionitis, puerperal sepsis, postnatal fever);
- Adverse effects of treatment;
- Maternal well-being;
- Maternal satisfaction.

Critical newborn outcomes considered were:

- Perinatal death (fetal and early neonatal deaths);
- Neonatal death;
- Fetal death or stillbirth;
- Severe neonatal morbidity (i.e. an illness in the neonatal period that is associated with a high risk of death or severe long-term disability among survivors, e.g. respiratory distress syndrome, intraventricular haemorrhage, neonatal infection, necrotising enterocolitis, chronic lung disease, periventricular leukomalacia, and retinopathy of prematurity);
- Birth weight (mean; low or very low);
- Infant or childhood death;
- Long-term morbidity (i.e. an illness occurring after the neonatal period that is associated with physical or behavioural impairment among survivors, e.g. cerebral palsy, developmental delay, intellectual, hearing, or visual impairment).

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

Name	Expertise contributed to guideline development	Declared Interest	Management of declared interest
GUIDELINE DEVELOPMENT GROUP			
Shabina ARIFF	Content expert and end-user (Obstetrics)	None	Not applicable
Elena ATEVA	Human rights expert	Project Lead for a White Ribbon Alliance-led health policy project (in collaboration with WHO and ICM), funded by USAID	The interest was declared to the group, and not considered a serious conflict that would warrant exclusion from GDG deliberations
Maria Laura COSTA	Content expert and end-user (Obstetrics)	None	Not applicable
Gary DARMSTADT	Content expert and end-user (Neonatology)	None	Not applicable
Bissallah EKELE	Content expert and end-user (Neonatology)	None	Not applicable
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Caroline HOMER	Content expert and end-user (Midwifery)	None	Not applicable
Sankar JEEVA	Content expert and end-user (Neonatology)	None	Not applicable
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Pisake LUMBIGANON	Content expert and end-user (Obstetrics)	None	Not applicable
Silke MADER	Representative of the affected population	None	Not applicable
Elizabeth MOLYNEUX	Content expert and end-user (Neonatology)	None	Not applicable
Ashraf NABHAN	Content expert and end-user (Obstetrics)	None	Not applicable
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Name	Expertise contributed to guideline development	Declared Interest	Management of declared interest
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Joshua VOGEL	Content expert, evidence synthesis, guideline methodology	None declared	Not applicable
Myfanwy WILLIAMS	Content expert, evidence synthesis, guideline methodology	None declared	Not applicable

Web Annex: Evidence-to-Decision Frameworks

WEB ANNEX	COMPARISON	LINK
2.0	Tocolytics compared to placebo or no tocolytics for delaying preterm birth and reducing adverse neonatal outcomes	https://apps.who.int/iris/bitstream/handle/10665/363130/9789240057241-eng.pdf

World Health Organization

human reproduction programme hrp

research for impact

UNDP · UNFPA · UNICEF · WHO · WORLD BANK