WHO guidelines on expanding contraceptive options

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Guideline Development Group

Faisal Abbas (National University of Sciences and Technology, Islamabad, Pakistan), Valeria Bahamondes (independent consultant, the United States of America [USA]), Harriet Chanza (Credo Community Support Group, Lilongwe, Malawi), Rodrica Comendant (Reproductive Training Center, Chisinau, Moldova), Galina Dikke (Medical Academy of Postgraduate Education, Moscow, the Russian Federation), Andy Gray (Centre for the AIDS Programme of Research in South Africa [CAPRISA], University of KwaZulu-Natal, Pretoria, South Africa), Lisa Haddad (Population Council, New York City, USA), Philip Hannaford (University of Aberdeen, the United Kingdom of Great Britain and Northern Ireland), Unnop Jaisamrarn (Chulalongkorn University, Bangkok, Thailand), Beena Joshi (National Institute for Research in Reproductive and Child Health [NIRRCH], India), Enriquito Lu (independent consultant, Manila, the Philippines), Philip Mbithi Muia (Kenya Medical Research Institute, Nairobi, Kenya), Ashraf Nabhan (Ain Shams University, Cairo, Egypt), Ingrid Sääv (Stockholm County Youth Clinics, Stockholm, Sweden), Farida Shah (International Confederation of Midwives, Islamabad, Pakistan), Aparna Sridhar (University of California, Los Angeles and International Federation of Gynecology and Obstetrics [FIGO], USA), Nandana Suresh (White Paper Academy Alappuzha, Kerala, India), Kun Tang (Vanke School of Public Health, Tsinghua University, China), Peace Samuel Umanah (International Youth Alliance for Family Planning, Abuja, Nigeria). WHO wishes to recognize the expertise and contribution of Katherine Curtis (independent consultant, Atlanta, USA) who was, until 20 January 2025, the co-chair of this GDG.

Evidence Synthesis Team

The guideline methodologist was Nancy Santesso (McMaster University, Toronto, Canada), and the members of the systematic review team leads for the ECO topics were: Yaolong Chen (Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical Sciences [2021RU017]), School of Basic Medical Sciences, Lanzhou University, China), Li Jiang (Hospital for Sick Children, Toronto, Canada), Shaalini Ramanadhan (Oregon Health and Science University, Portland, USA), Sarita Sonalkar (University of Pennsylvania, Philadelphia, USA) and Tesfaye Tufa (St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia). Sesilia Shirima (Young and Alive, the United Republic of Tanzania) conducted the youth engagement survey. Sameera Mokkarala (Planned Parenthood Association of America, USA) contributed to the scoping review.

External Review Group

Sylvia Ayieko (University of Iowa, Iowa City, USA), Nurun Nahar Begum (Former Line Director, Directorate General of Family Planning, Dhaka, Bangladesh), Blami Dao (Université Nazi Boni, Institut Supérieur des Sciences de la Santé [INSSA], Ouagadougou, Burkina Faso), Nasser El Kholy (Ain Shams University, Cairo, Egypt),

Neena Malhotra (All India Institute of Medical Sciences, New Delhi, India), Richard Mugahi (Ministry of Health, Kampala, Uganda), Phanupong Phutrakool (Chula Data Management Center, Bangkok, Thailand), Hanna Teklu (St Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia) and Mariano Salazar Torres (Karolinska Institute, Stockholm, Sweden).

Observers

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WHO Guideline Steering Group

WHO is also grateful for the input to this guideline from the following WHO Guideline Steering Group (GSG) members from a range of departments in the Division of Health Promotion, Disease Prevention and Control at WHO headquarters in Geneva, Switzerland: Department of Sexual and Reproductive, Maternal, Child and Adolescent Health and Ageing (LHR) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP): Pascale Allotey (Director); James Kiarie (Unit Head), Moazzam Ali, Rita Kabra, Asantesana Kamuyango, Nancy Kidula, Petrus Steyn and Nandita Thatte (Contraception and Fertility Care Unit [CFC]); Mercedes Bonet (Maternal and Perinatal Health Unit); Kidist Gizachew, Caron Kim (Prevention of Unsafe Abortion Unit); Aasa Hanna Mari Nihlén (Rights and Equality Across the Lifecourse Unit); Tigest Tamrat (Sexual and Reproductive Health Integration in Health Systems Unit); and Manjula Narasimhan (Sexual, Reproductive and Newborn Health Unit).

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Coordination and writing

Overall coordination for guideline development was provided by the WHO Secretariat Team, comprising James Kiarie (Unit Head), Asantesana Kamuyango and Nancy Kidula (responsible technical officer), both from the CFC Unit in WHO LHR/HRP. The first draft of the guideline was written by Mary Lyn Gaffield (Health Guideline Advisors, Auxonne, France), Nancy Kidula (CFC Unit) and Nancy Santesso (Grading of Recommendations, Assessment, Development and Evaluation [GRADE] methodologist, McMaster University, Toronto, Canada). Drafts were reviewed and input was provided by members of the GDG, EST, ERG and WHO GSG. The authorship of the five systematic reviews providing summarized evidence for this guideline was led by the EST, with the full set of coauthors reflected in the respective papers as published in the BMJ Sexual and Reproductive Health 2026 supplement issue (https://doi.org/10.1136/bmjsrh-2026). The GRADE evidence-to-decision tables and expertise on GRADE methodology were provided by Nancy Santesso (McMaster University, Toronto, Canada).

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Abbreviations

BMI	body mass index
CI	confidence interval
CIRE	Continuous Identification of Research Evidence process
COCs	combined oral contraceptives
DMPA	depo medroxyprogesterone acetate
DVT	deep vein thrombosis
EC	emergency contraception
ECO	expanding contraceptive options
ERG	External Review Group
EST	Evidence Synthesis Team
EtD	evidence-to-decision
ETG	etonogestrel
GDG	Guideline Development Group
GRADE	Grading, Recommendations, Assessment, Development and Evaluation
HRP	UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction
INN	International Non-proprietary Name
IUD	intrauterine device
LNG	levonorgestrel
MEC	*Medical eligibility criteria for contraceptive use guideline*
OR	odds ratio
PICO	population, intervention, comparator and outcome
Quin-Quin	quinestrol-quingestanol
Quin-LNG	quinestrol-levonorgestrel
Quin-NG	quinestrol-norgestrel
RCT	randomized controlled trial
SPR	Selected practice recommendations for contraceptive use guideline
VTE	venous thromboembolism

Executive summary

Introduction

The *World Health Organization (WHO) expanding contraceptive options (ECO) guideline* aims to improve access to and quality of family planning services by providing evidence-based recommendations on emerging contraceptive methods and service delivery practices with global potential. Expanding the range of contraceptive methods and service delivery practices can improve access to a wider range of contraceptive options for women, girls, men and boys, and couples. This is particularly important in settings with limited access to and choice of contraceptive methods, including in many low- and middle-income countries. Enhancing the quality of family planning services is essential for reducing maternal mortality and morbidity and advancing progress towards the Sustainable Development Goals.

As new contraceptive methods and alternative approaches to the use of existing methods become available, Member States require evidence-based guidelines to support decisions regarding their incorporation into national family planning policies, programmes and service delivery protocols, especially when specific recommendations are not yet available in WHO published guidelines. These new methods and/or practices may be approved by local health authorities but have yet to be prequalified by a WHO-recognized stringent regulatory authority and may not be in the WHO Model List of Essential Medicines. It is envisaged that contraceptive methods and practices in the WHO ECO guideline that are either recommended or suggested for inclusion into national contraceptive mixes may be incorporated into future updates of the WHO *Medical eligibility criteria for contraceptive use (MEC)* and WHO *Selected practice recommendations for contraceptive use* (SPR) guidelines once they meet the inclusion criteria for these normative guidelines. This would facilitate WHO prequalification and consideration for addition to the WHO Model List of Essential Medicines.

Target audience

This guideline is intended for policy-makers, family planning programme managers, health workers and the scientific community. Recommendations in the guideline are intended to inform national family planning and reproductive health programmes regarding the inclusion of specific emerging contraceptives and emerging contraceptive usage practices into their national contraceptive method mix.

Guideline development methods

The Guideline Development Group (GDG) convened by WHO consisted of 20 individuals from 16 countries, representing all six WHO regions. The GDG included experts in family planning, midwifery, gynaecology, obstetrics, epidemiology, pharmacology, gender, policy-making, health systems, health communications, health economics, guideline methodology and evidence synthesis. Representatives of key stakeholders and users were also part of the GDG membership. The Acknowledgement section lists all GDG members, and their declarations of interests are described in Annex 1. The meetings were held at WHO headquarters in Geneva, Switzerland, 11–13 June 2024 and 17–19 June 2025.

The GDG prioritized for consideration five topics for the development of the ECO guideline: three topics concerned the inclusion of new contraceptive methods within WHO guidance (ormeloxifene, quinestrol-containing pills and mifepristone for emergency contraception [EC]) and two topics concerned new contraceptive practices (continuous or extended use of

combined oral contraceptive pills and extended duration of etonogestrel [ETG] implant use).

The GDG applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to consider the overall certainty of the available evidence, and the GRADE evidence-to-decision (EtD) framework to develop recommendations. The GDG defined the strength of recommendations as strong or conditional and the direction as for or against implementation.

At a minimum, this guideline will be reviewed every five years with periodic updates as new contraceptive methods and delivery practices become available and utilized in WHO Member States. Any change in recommendation will be promptly communicated to Member States and partners to guide policy and programming and made available on the WHO web pages for the Department of Sexual and Reproductive Health and Research at www.who.int/hrp and www.who.int/health-topics/contraception. WHO encourages research aimed at addressing key unresolved issues related to contraceptive methods and practices presented in this guideline. WHO also invites comments and suggestions for improving this guideline.

Summary of recommendations

Recommendations reviewed for the ECO guideline	
Recommendation	*Strength of recommendation and certainty of evidence*
Mifepristone for EC	
WHO recommends adding mifepristone to the method mix for EC, as a single dose between 10 and 50 mg. *Remarks:* the availability of mifepristone dosage forms may differ across settings and countries. A dose between 10 and 25 mg may be preferred if available. EC pills are taken as soon as possible after unprotected sex and within five days.	**Strong recommendation** Moderate-certainty evidence
Ormeloxifene	
WHO suggests against adding ormeloxifene to the contraceptive method mix for women of reproductive age. *Remarks:* high-quality evidence is needed to confirm the efficacy and safety of ormeloxifene as a contraceptive.	**Conditional recommendation** Very low-certainty evidence

Recommendations reviewed for the ECO guideline	
Recommendation	*Strength of recommendation and certainty of evidence*
Quinestrol-containing pills: quinestrol-quingestanol, quinestrol-norgestrel and quinestrol-levonorgestrel	
WHO recommends against adding quinestrol-quingestanol to the contraceptive method mix for women of reproductive age.	**Strong recommendation** Very low-certainty evidence
WHO recommends against adding quinestrol-norgestrel to the contraceptive mix for women of reproductive age.	**Strong recommendation** Very low-certainty evidence
WHO suggests against adding quinestrol-levonorgestrel to the contraceptive method mix for women of reproductive age.	**Conditional recommendation** Low-certainty evidence
Remarks: where quinestrol-containing products are being used, rigorous pharmacovigilance is needed to monitor safety. High-quality evidence about its efficacy and safety is needed.	
Continuous or extended use of COCs	
WHO suggests that COCs can be used for extended durations up to six months or continuously up to one year, as well as their cyclical use for contraception in women of reproductive age.	**Conditional recommendation** Low-certainty evidence
Remarks: extended-cycle regimen is defined as taking active combined hormonal contraceptive pills continuously for more than 28 days, followed by a planned hormone-free interval. Extended use may be for flexible or fixed duration.	
A continuous regimen is defined as taking active combined hormonal contraceptive pills every day without any breaks in daily pill-taking (no hormone-free interval).	
Extended use of ETG contraceptive implants	
WHO suggests ETG contraceptive subdermal implants can be used for up to five years, as an option in line with updated manufacturers' approved duration of five years.	**Conditional recommendation** Very low-certainty evidence

COCs: combined oral contraceptives; EC: emergency contraception; ETG: etonogestrel.

1 Introduction

1.1 Background

Universal access to high-quality sexual and reproductive health services, and specifically the recognition of family planning/contraception as a key strategy for reducing maternal and child mortality, remains a global priority. While the number of women of reproductive age using modern contraceptive methods increased by 87% between 1990 and 2022 (from 467 million to 874 million), there are still 164 million women wanting to delay or avoid pregnancy who are not using contraception and thus have an unmet need for family planning. Addressing unmet need for family planning and assuring that there are laws and regulations that guarantee women and girls' access to family planning remains critical in reaching targets outlined in key global health agendas (e.g. Sustainable Development Goals 3.7.1 and 5.6.2; the Global Strategy for Women's, Children's and Adolescents' Health 2016–2030).

Since 1996, the Department of Sexual and Reproductive, Maternal, Child and Adolescent Health and Ageing (LHR) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) at the World Health Organization (WHO), in collaboration with relevant partners, have produced the *Medical eligibility for contraceptive use guideline* (MEC) *(1)* and the *Selected practice recommendations for contraceptive use guideline* (SPR) *(2)*. These evidence-based guidelines inform and support the efforts of Member States to implement family planning programmes. Recommendations in these guidelines focus on contraceptive methods that are approved by a globally recognized regulatory authority and use that follows product label instructions. Specifically, the MEC provides recommendations on the safety of various contraceptive methods for use in the context of specific health conditions or characteristics, and the SPR includes recommendations on how to use contraceptive methods safely and effectively once they are deemed medically appropriate. The overarching goal of these guidelines is to remove unnecessary medical barriers to contraception, while ensuring safety, fostering choice and safeguarding correct use.

As new contraceptive methods and different ways of using existing methods become available, Member States need evidence-based guidance on whether to include or exclude these methods and the alternative usage practices into their national contraceptive method mix policies, family planning programmes and service delivery protocols, especially when specific recommendations are not available in the WHO published guidelines. These contraceptive methods and/or practices may be approved by local health authorities but have yet to be prequalified by a stringent regulatory authority and may not be in the WHO Model List of Essential Medicines. In the *WHO expanding contraceptive options (ECO) guidelines*, WHO responds to this need by providing evidence-based guidance on the effectiveness, safety and acceptability of these methods and recommends whether or not they can be included in the contraceptive method mix and used by national family planning programmes.

It is envisaged that contraceptive methods and practices in this guideline that are either recommended or suggested to be added into a national contraceptive mix, would be integrated into future editions of the WHO MEC and SPR once they meet the thresholds for these normative guidelines (see Fig. 1 on how the ECO guideline intersects with the MEC and SPR). Plus, their inclusion in these guidelines would facilitate prequalification by WHO and addition to the WHO Model List of Essential Medicines. Additionally, the ECO guideline provides recommendations against certain methods and practices that may be in use but should not be adopted until evidence demonstrating their efficacy and safety becomes available.

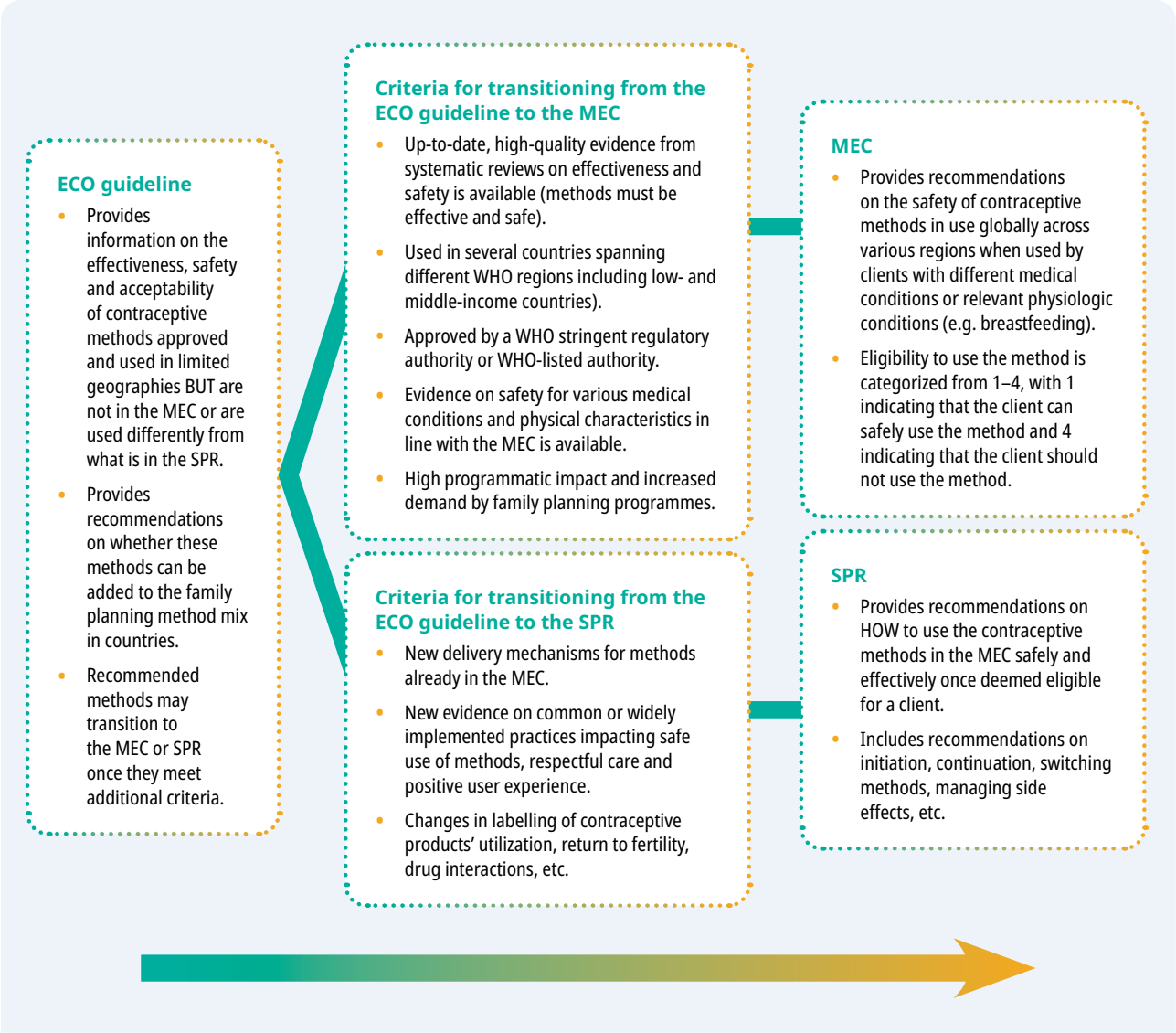
1.2 Purpose

The ECO guideline aims to improve access to and quality of family planning services by providing evidence-based recommendations on emerging contraceptive methods and alternative contraceptive use practices with potential for global application. Expanding the range of available contraceptive methods and use practices can increase contraceptive choice for women, girls and couples. This is particularly important in settings with limited access to and choice of contraceptive methods including in many low- and middle-income countries. Strengthening the quality of family planning services contributes to improved sexual and reproductive health outcomes, including reductions in maternal morbidity and mortality, and supports progress towards the Sustainable Development Goals across the themes of people, planet, prosperity, peace and partnership.

1.3 Scope and target audience

The intended audience for this guideline includes policy-makers, family planning programme managers, health workers and the scientific community. Recommendations presented within the ECO guideline are intended to inform national family planning and reproductive health programmes regarding the inclusion – or exclusion – of specific contraceptives and alternative contraceptive usage practices into their national contraceptive method mix.

Fig. 1 Relationship of the ECO guideline with the MEC and SPR guidelines



ECO: *WHO expanding contraceptive options guideline*; MEC: *WHO medical eligibility criteria for contraceptive use guideline*; SPR: *WHO selected practice recommendations for contraceptive use guideline.*

2 Methods

In recent years, Member States and non-state actors have approached WHO with requests for guidance on the safety and effectiveness of novel or new usage of a contraceptive method that are not included in the WHO MEC and SPR guidelines but are being used in some WHO Member States *(1,2)*. Contraceptive methods and usage practices within the ECO guideline will need to fulfil the following criteria to be included in the MEC guideline: they are used globally in many countries (including low- and middle-income countries); they have been approved by a stringent regulatory authority; they have evidence of safety in various medical conditions or physiologic characteristics; there is a demonstrated demand from family planning programmes; and they have high programmatic impact (see Fig. 1). The ECO guideline – a new WHO guideline – was developed in response to these requests following the guideline development requirements outlined in the WHO *handbook for guideline development, 2nd edition (3)*.

The groups responsible for the development of this guideline include a WHO Secretariat, an Evidence Synthesis Team (EST) (including a guideline methodologist), a Guideline Development Group (GDG) and an External Review Group (ERG). For the names of the members of all these groups, see the Acknowledgements, and for details of declared academic and financial interests see Annex 1.

Development of the guideline involved several steps: 1) preparation of a scoping review of studies to identify existing evidence on emerging contraceptive methods and uses; 2) formation of groups responsible for the development of the guideline; 3) convening a GDG scoping meeting to prioritize which topics should be addressed in the guideline; 4) conducting systematic reviews of the published literature and preparing Grading, Recommendations, Assessment, Development and Evaluation (GRADE) evidence profiles and evidence-to-decision (EtD) tables; 5) convening a final GDG meeting to formulate the recommendations; 6) external review and 7) approval of the guidelines by WHO.

2.1 Scoping

A scoping review was undertaken to identify published evidence on (a) contraceptive methods not included in the MEC 5th edition but registered in at least one Member State; and (b) contraceptive methods included in the 5th edition of the MEC but used differently from what is described in the 3rd edition of the SPR. Prior to conducting the scoping review, an online survey was conducted in English, French and Spanish among WHO Member States and various WHO partners from 1 October to 30 November 2023, to ascertain which contraceptive methods, other than those already cited in the WHO normative guidelines, are in use. The survey yielded responses from 958 individuals in 141 Members States across six continents. Additionally, suggestions from subject-matter experts and inquiries from Member States also informed which contraceptive methods should be included in the review.

The following methods were identified from the stakeholder survey and interactions with Member States and key partners:

- Methods not in the MEC: ormeloxifene, quinestrol/quingestanol, mifepristone for emergency contraception (EC), levonorgestrel intrauterine device (LNG- IUD) for EC, pericoital contraception.
- Methods used differently than stated in the SPR: extended use of LNG and etonogestrel (ETG) implants, extended use of depo medroxyprogesterone acetate (DMPA), extended and continuous use of combined oral contraceptives (COCs) and extended use of the progesterone vaginal ring.

The PubMed and EMBASE bibliographic databases were searched, using terms for methods identified by the online survey or expert informants, from database inception through December 2023. Quantitative, qualitative and mixed-methods studies investigating the efficacy, safety and/or acceptability of the contraceptive methods were included. The review protocol was registered with Open Science Framework (https://osf.io/h9nj3). Results of the scoping reviews are published in Mokkarala et al. *(4)*.

2.2 Framework to prioritize guideline topics

The findings of the scoping review were presented to the GDG during the first of two GDG meetings. At the first scoping meeting, held 11–13 June 2024, the GDG agreed on a framework to prioritize topics to be discussed during the second GDG meeting. The prioritization framework contained three possible actions: 1) proceed to full systematic review and include in the ECO guideline, 2) do not proceed to systematic review but recommend additional research as the method looks promising, and 3) do not proceed with any further action (see Box 1).

To undertake this exercise, the GDG first evaluated whether there was evidence regarding the efficacy, safety and acceptability of the method. Depending on the available evidence, the GDG then determined whether the contraceptive method had important implications for family planning programmes and/or expansion of the contraceptive method mix. If both of these criteria were met, the GDG recommended that a systematic review should be conducted. If implications for programmes and expansion of the method mix existed, but evidence did not appear to be available regarding efficacy, safety and acceptability, the GDG advised that additional research should be pursued. If evidence about a method's efficacy, safety and acceptability were available but implications for programmes and the expansion of the method mix were deemed to be minimal, a systematic review was not recommended. If evidence on the efficacy, safety and acceptability of a method was not available and implications for programmes and the expansion of the method mix were deemed to be minimal, no further action was recommended.

2.3 Prioritized guideline topics

Based on the findings of the scoping review and plenary discussions and debate, the GDG prioritized three emerging contraceptive methods and two contraceptive usage practices to include in the new guideline. And as a result, the GDG proposed the following recommendation questions for further evaluation:

1. Should mifepristone be added to the contraceptive method mix for EC (and at what dose) for women of reproductive age?
2. Should ormeloxifene be added to the contraceptive method mix for women of reproductive age?
3. Should quinestrol-containing pills be added to the contraceptive method mix for women of reproductive age?
4. Should COCs at extended or continuous duration versus cyclical use be used in women of reproductive age?
5. Should ETG contraceptive subdermal implants be used up to five years versus three years in women of reproductive age?

In addition, the GDG determined the outcomes to be assessed by each systematic review, with the same effectiveness and acceptability outcomes used for all questions, and the safety outcomes varying according to the question asked (see Box 2).

Box 1 Framework for prioritization of topics for systematic review

Evidence available of efficacy, safety and acceptability?	Important implications for programmes and expansion of method mix?	GDG decision
Yes	Yes	Systematic review recommended
Yes	No	Systematic review not recommended
No	Yes	Further research recommended
No	No	No further action recommended

GDG: Guideline Development Group.

2.4 Evidence identification and synthesis

For each recommendation question, evidence synthesis teams conducted new or updated existing systematic reviews. A protocol for each review was developed, guided by the outcomes listed in Box 2, and registered in the International Prospective Register of Systematic Reviews (PROSPERO) open access online database. The systematic reviews are available as open access in the *BMJ Sexual and Reproductive Health* 2026 supplement issue or on request via email to WHO (srhcfc@who.int). In general, multiple databases (e.g. PubMed and Cochrane databases) were searched for studies published in any language from database inception to: 21 October 2024 (COCs), 27 November 2024 (mifepristone), 1 December 2024 (quinestrol) and 30 June 2025 (ormeloxifene). In addition, studies published from 1 January 1996 to 8 November 2024 were searched for ETG. Reference lists and direct communications with experts in the field were also used to identify other studies and data.

The risk of bias for each study included in a systematic review was assessed by review authors using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) *(5)* and a modified version of the Cochrane tool to assess risk of bias in non-randomized studies (ROBINS-I) *(6)*. GRADE evidence profiles were prepared, and the GRADE approach was used to assess the certainty of the evidence as high, moderate, low or very low; and communicated as: the intervention has an effect, likely has an effect, may have an effect, or it is uncertain, respectively *(7)*. The systematic review reports were made electronically available to all GDG members prior to the second GDG meeting.

Additional information about the feasibility, resources and equity issues were also summarized from the systematic reviews. Results from a global systematic review of qualitative and quantitative studies on the values and preferences of contraceptive users *(8)* as well as voices of young people who participated in a global series of online sessions, workshops and webinars conducted from November 2024 to July 2025, were presented to the GDG. More than 5000 youth representing all WHO regions, including youth from low- and middle-income countries (e.g. Democratic Republic of the Congo, Ghana, Nepal, Uganda, United Republic of Tanzania and Zimbabwe) provided their views during interactive sessions on Facebook, TikTok, Instagram, LinkedIn, Club House and WhatsApp. The report of the youth consultation is available on request via email to WHO (srhcfc@who.int).

Box 2 Outcomes for systematic reviews

Type of outcome	Outcomes of interest
Effectiveness outcomes	Pearl Index,[a] pregnancy rate,[b] ectopic pregnancy
Safety outcomes	Severe adverse events (e.g. venous thromboembolism, cardiovascular outcomes, abnormal liver function, fetal birth defects) Side effects (e.g. headaches, nausea, cramping or pain, early/delayed menses, abnormal uterine bleeding, amenorrhoea)
Acceptability outcomes	Acceptability (satisfaction), return to fertility, discontinuation

[a] The Pearl Index is defined as the number of pregnancies per 100 woman-years using a specific contraceptive method. The Pearl Index represents the number of unintended pregnancies that occur while using a contraceptive method over a year of usage for 100 women.

[b] Pregnancy rate refers to the overall rate of pregnancies in a population of reproductive age women (15–44 years of age). Pregnancy rate can be calculated as: total number of pregnancies (includes live births + induced abortions + fetal deaths and stillbirths) divided by the number of women aged 15–44 years, then multiplied by 1000.

2.5 Decision-making during the final GDG meeting

WHO convened the final GDG meeting 17–19 June 2025, at WHO headquarters in Geneva, Switzerland, to determine and finalize the recommendations. Members of the GDG submitted declaration of interest forms to the WHO Secretariat and six individuals declared a conflict of interest relevant to the ECO guideline. The WHO Secretariat reviewed all declaration of interest forms and found one participant, who had disclosed a potentially significant conflict of interest related to the topic of ormeloxifene, which was deemed sufficient to preclude her from participating in the discussions and development of the recommendation relevant to ormeloxifene. The remaining GDG members had no conflicts of interest sufficient to preclude them from participating in the deliberations or development of recommendations. For details of the declared interests see Annex 1.

The GDG considered all the criteria in the GRADE EtD framework when making its recommendations: evidence for benefits and harms and the certainty, the values and preferences of contraceptive users and health workers, acceptability to users, cost and resource implications, feasibility of implementation and equity. The GDG took a population perspective when making the recommendations and considered that populations should have access to a wide range of contraceptive options, without misinformation or financial or policy barriers, and can base their decisions for implementation on their own unique temporal, societal and cultural context *(8)*.

To formulate recommendations, the GDG applied the following taxonomy: recommendations were either "strong" or "conditional" and "for" or "against" implementation and use. In the ECO guideline, a strong recommendation is presented as recommends and a conditional recommendation is presented as suggests (see Box 3).

Through consensus during the in-person meeting, the GDG developed four of the five recommendations. Voting was required to achieve a decision on the recommendation for ormeloxifene. All GDG members eligible to participate in the discussions and decisions agreed to the final direction and strength of the ormeloxifene recommendation. The wording and decisions presented in the EtD frameworks were completed through discussions during the in-person June 2025 meeting and electronically via teleconference on 17 July 2025 and email discussions through 7 October 2025 (see Annex 2).

A draft of the entire ECO guideline document was sent to the ERG, which comprised eight experts who did not participate in the GDG meeting. The WHO Secretariat reviewed all declarations of interests and found no conflicts of interest sufficient to preclude any ERG members from reviewing and commenting on the entire document. For details of their declarations of interests see Annex 1. Comments received from these reviewers were addressed and incorporated into this guideline as appropriate. The final version of this document was approved by the Guidelines Review Committee on 11 March 2026.

Box 3 Definitions of strong and conditional recommendations

Strong recommendation (WHO recommends)

- The GDG judged that the desirable consequences clearly outweigh the undesirable ones (FOR).

  or
- The GDG judged that the undesirable consequences clearly outweigh the desirable ones (AGAINST).

- A strong recommendation TO ADD a method indicates the method can be adopted as policy.

  or
- A strong recommendation AGAINST ADDING a method indicates the method should not be adopted as policy.

- Users should adhere to the contraceptive usage practices that WHO denotes as a strong recommendation FOR the practice to safeguard high-quality family planning care.

  or
- Users should not adhere to contraceptive usage practice that WHO determined as a strong recommendation AGAINST the practice to safeguard high-quality family planning care.

Conditional recommendation (WHO suggests)

- The GDG judged that the desirable consequences probably outweigh the undesirable consequences (FOR).

  or
- The GDG judged that the undesirable consequences probably outweigh the desirable consequences (AGAINST).

- A conditional recommendation TO ADD or AGAINST ADDING a method indicates the method may be adopted as policy. However, different choices may be appropriate for some individuals or settings depending on considerations such as resources, feasibility or availability.

- New evidence may result in a change to the balance of risks to benefits.

GDG: Guideline Development Group.

3 Recommendations

3.1 Mifepristone for EC

WHO recommends adding mifepristone to the method mix for EC, as a single dose between 10 and 50 mg.

Remarks: the availability of mifepristone dosage forms may differ across settings and countries. A dose between 10 and 25 mg may be preferred if available. EC pills are taken as soon as possible after unprotected sex and within five days.

Strong recommendation, moderate-certainty evidence

3.1.1 Background

EC remains an important tool for individuals seeking to prevent pregnancy. Unintended pregnancy affects an estimated 121 million people worldwide *(9)*. When individuals are not using a consistent contraceptive method, do not have access to contraception, have a regular method that fails or are victims of sexual violence, EC can be the only option to reduce the risk of becoming pregnant. EC oral methods that are currently used and included in clinical guidelines are ulipristal acetate, LNG and COCs – often referred to as the Yuzpe method *(10, 11)*. The copper intrauterine device (IUD) is also used for EC.

Mifepristone is a norethindrone derivative that strongly binds to progesterone and glucocorticoid receptors, functioning as an antagonist. Mifepristone has been found to delay or prevent ovulation via this progesterone receptor antagonism. Mifepristone as EC is approved and utilized in a few countries including Armenia, China, the Russian Federation and Ukraine *(12)*. The dosing regimen of mifepristone as EC varies, with doses ranging from 10 to 600 mg taken within 120 hours of unprotected intercourse.

The GDG examined the following key question: "Should mifepristone be added to the contraceptive method mix for EC (and at what dose)?"

3.1.2 Balancing desirable and undesirable effects

Evidence from a recent systematic review of 87 randomized controlled trials (RCTs) was included *(13)*. The literature search was performed through December 2024. The review included studies comparing mifepristone to other methods of EC (COCs [Yuzpe method], LNG oral pills, and copper IUDs [as EC]). No studies comparing mifepristone to ulipristal acetate were identified. Studies were included if the population was women seeking EC for the prevention of pregnancy within 120 hours of unprotected intercourse.

Results showed that compared with LNG, mid-dose mifepristone (25–50 mg) likely resulted in 12 fewer pregnancies per 1000 women (risk ratio [RR] 0.67, 95% confidence interval [CI]: 0.49 to 0.91). Compared to LNG, low-dose mifepristone (10–25 mg) resulted in 5 fewer pregnancies per 1000 women (RR 0.73, 95% CI: 0.59 to 0.90). Compared with COCs (Yuzpe regimen), any dose of mifepristone assessed was found to likely result in 22 fewer pregnancies per 1000 women (RR 0.14, 95% CI: 0.05 to 0.41).

In terms of undesirable effects experienced per 1000 women, there was moderate-certainty evidence. Mid-dose mifepristone, when compared with LNG likely resulted in 91 fewer side effects including nausea, vomiting and spotting (RR 0.55, 95% CI: 0.39 to 0.76) and likely resulted in 31 more delayed menses events (RR 1.29, 95% CI: 1.01 to 1.64).

When low-dose mifepristone was compared with LNG, mifepristone likely reduced side effects (RR 0.26, 95% CI: 0.17 to 0.38) and slightly increased delayed menses (RR 1.52, 95% CI: 1.11 to 2.08).

When comparing mifepristone to Yuzpe, mifepristone likely reduced side effects (RR 0.89, 95% CI: 0.83 to 0.95), and increased delayed menses (RR 2.83, 95% CI: 2.31 to 3.47).

3.1.3 Other considerations

There is moderate certainty in the results for acceptability: mifepristone was compared with other oral methods (LNG and Yuzpe) and found to probably increase satisfaction (RR 1.09, 95% CI: 1.05 to 1.13).

Mifepristone costs can be variable, and it is not currently widely manufactured or available. Because the other primary use of mifepristone is for medical abortion, political and legal contexts in various countries may influence access. The GDG noted that there may be some concerns related to potential for misuse, however these could be overcome by education, packaging or promotion.

The GDG discussed the need for programmatic monitoring of the use of mifepristone for EC. Countries may need to determine how to make it available (e.g. over the counter or prescribed) and whether the costs are covered. The GDG also noted that registration and inclusion in essential medicines lists may motivate production and access.

3.1.4 Justification

The GDG made a strong recommendation for the inclusion of mifepristone in the method mix for EC. Overall, there is moderate certainty in the evidence for the effects of mifepristone; mifepristone is likely to be as effective and safe as other emergency contraceptive methods. Providing mifepristone instead of other EC methods may be more cost-effective in contexts where the cost of mifepristone is lower and thereby increase equitable access to EC if made widely available. It is probably as acceptable to women and clinicians as other methods, and probably feasible to provide. As with all emergency contraceptive methods, the provision of quality information for users and health professionals will be necessary to ensure appropriate use when added to the contraceptive method mix.

3.1.5 Implementation considerations

When implementing this recommendation, the GDG underscored the paramount importance of the right to contraceptive choice. Further, the GDG emphasized the imperative of addressing the following overarching issues when adding mifepristone for EC to national programmes.

- Informed consent
- Elements of quality of care
- Essential screening procedures for administering EC pills
- Provider training skills
- Referral and follow-up care for contraceptive use, as appropriate.

In addition, the GDG advised that WHO Member States should specifically consider the following when implementing mifepristone for EC:

- The cost of mifepristone varies depending on the dosage in countries; current estimates range from US$ 0.90–1.00 for 25 mg and US$ 1.20–1.35 for 50 mg.

3.2 Ormeloxifene

WHO suggests against adding ormeloxifene to the contraceptive method mix for women of reproductive age.

Remarks: high-quality evidence on the efficacy and safety of ormeloxifene as an oral contraceptive is needed.

Conditional recommendation, very low-certainty evidence of effects

3.2.1 Background

Ormeloxifene, also known as centchroman, is a non-hormonal selective estrogen receptor modulator (SERM) developed in India as a weekly oral contraceptive. Ormeloxifene (marketed under various brands including Saheli, Choice-7 and Chhaya) is commonly used as a 30 mg tablet taken twice weekly for 12 weeks, then once weekly. Its contraceptive action is believed to occur by disrupting the synchronization between the embryo and the endometrium, thereby preventing implantation. Ormeloxifene is currently used only in India, where it was approved by the Drug Controller General of India (DCGI) for use in 1991. In 2016, it was incorporated into India's national programme and has been on the National List of Medicines of India since 2022. Ormeloxifene is currently not in the WHO Model List of Essential Medicines.

The GDG examined the following key question: "Should ormeloxifene be added to the contraceptive method mix for women of reproductive age?"

3.2.2 Balancing desirable and undesirable effects

A systematic review of evidence on the safety and effectiveness of ormeloxifene was conducted. Multiple bibliographic databases were searched from database inception through 30 June 2025. Fourteen studies met the inclusion criteria *(14–27)*. Of these studies, three were RCTs, two were prospective comparative studies and nine were case series.

Eleven of the 14 included studies reported data on the effectiveness of ormeloxifene as a regular contraceptive *(15–25)* measured using the Pearl Index and the number of pregnancies recorded during the study period. The Pearl Index varied between 0.48 and 4.2 pregnancies per 100 woman-years. Method failure rates ranged from 0% to 4%, while user-related failure rates were between 0.8% and 10.1%. Based on the comparative and non-comparative studies, the GDG agreed that the number of pregnancies with ormeloxifene may be similar to the percentages with other oral contraceptive pills or with injectable contraceptives, which usually ranged from 4% to 7% for typical use, but the evidence is uncertain.

All 14 studies assessed the safety of the drug, including the occurrence of serious adverse events of interest (hepatotoxicity, thromboembolic events, hypertension, endometrial hyperplasia, uterine prolapse, loss of bone density, the effect on breastfeeding and fetal birth defects). One study (n = 3139 women) with a 24-month follow-up reported two cases of endometrial hyperplasia within six months of ormeloxifene use *(24)*. Another study (n = 247) followed the number of women who reported reduced milk production at one, three and six months among women who used ormeloxifene in the postpartum period *(20)*. According to this study, 5.7%, 2.7% and 2% of women reported a reduction in milk production at one, three and six months, respectively.

All 14 studies reported one or more side effects. The most commonly reported was menstrual irregularity – with delayed menstrual cycles, light menstrual flow and amenorrhoea the most frequently recorded irregularities. Menstrual irregularity was also found to be the major reason for discontinuation of ormeloxifene, with some studies observing up to 31.5% discontinuation due to the menstrual irregularity *(25)*. However, none of these studies reported menstrual irregularities that required intervention or treatment, such as treatment for anaemia or blood product transfusion.

One study (n = 280) compared irregular bleeding between ormeloxifene and COCs and showed a higher number of irregular cycles in the ormeloxifene group (11.1% vs 7.5%) *(16)*. This finding is consistent with another study (n = 240) which showed a higher number of delayed cycles (19.2% vs 5.8%), light flow (22.2% vs 7.77%) and amenorrhoea (3.3% vs 0%) in the ormeloxifene group compared to the COCs group *(15)*.

The GDG discussed whether studies including women with other conditions (e.g. postmenopausal women) receiving ormeloxifene could be included to provide evidence for undesirable effects. The GDG agreed not to include these studies as the population would be too indirect to inform the safety outcomes (e.g. differences in hormonal levels may influence adverse effects).

Regarding undesirable effects, the GDG noted that reports of side effects were inconsistent between the two comparative studies. It judged the body of evidence on the occurrence of adverse events as uncertain. Because the publicly available peer-reviewed reports and the manufacturer's report (which was shared with WHO for the meeting's deliberations) did not discuss or present any severe adverse events, the GDG was unable to interpret whether or not there were any (or no) severe adverse events associated with ormeloxifene use.

3.2.3 Other considerations

Five studies reported on the method satisfaction and acceptability of ormeloxifene compared with other contraceptive methods. In general, these studies found slightly higher levels of satisfaction among women using ormeloxifene versus women using other methods (such as COCs or IUDs). Overall satisfaction rates among ormeloxifene users across the five studies ranged between 75% and 95%. The GDG noted that ormeloxifene is very low cost in India or may be provided at no cost to women. Ormeloxifene needs to be taken once weekly, making it feasible. It also appears feasible to distribute – its use has increased over time in India and is now used by approximately 2 million people. During the in-person meeting, the GDG was unable to reach consensus on this recommendation because of the lack of data for adverse events in practice. Voting was required to achieve the final decision. Ultimately all GDG members eligible to participate in the discussions and decisions agreed to the final direction and strength of the recommendation.

3.2.4 Justification

The GDG made a conditional recommendation against the inclusion of ormeloxifene in the method mix for women of reproductive age. Overall, the GDG determined that the evidence for ormeloxifene is of very low-certainty and suggests that its effect on the prevention of pregnancy and its side effects are similar to other COCs, but the evidence is uncertain. The effect on adverse events is unknown due to the very low quality of reporting and presentation of the safety data. The cost of ormeloxifene is very low (and currently can be provided at no cost to users) in India which may increase equitable access to contraceptives, and evidence suggests that it is acceptable to individuals and feasible given the once weekly dose schedule.

Since the effects on benefits is uncertain, and the inability to assess adverse events with the current evidence available is a major concern, a conditional recommendation not to add it to the contraceptive method mix was made. High-quality evidence on its efficacy and safety is needed before considering adding it to the contraceptive method mix.

3.2.5 Implementation considerations

As the GDG formulated a conditional recommendation against adding ormeloxifene into national programmes' contraceptive method mix, implementation considerations were not discussed.

3.3 Quinestrol-containing pills: quinestrol-quingestanol, quinestrol-norgestrel and quinestrol-levonorgestrel

WHO recommends against adding quinestrol-quingestanol (Quin-Quin) to the contraceptive method mix for women of reproductive age.

Strong recommendation, very low-certainty evidence

WHO recommends against adding quinestrol-norgestrel (Quin-NG) to the contraceptive mix for women of reproductive age.

Strong recommendation, very low-certainty evidence

WHO suggests against adding quinestrol-levonorgestrel (Quin-LNG) to the contraceptive method mix for women of reproductive age.

Conditional recommendation, low-certainty evidence

Remarks: where quinestrol-containing products are being used, rigorous pharmacovigilance is needed to monitor safety. High-quality evidence about its efficacy and safety is needed.

3.3.1 Background

Quinestrol is a 3-cyclopentylether of ethinylestradiol that has been available in a once-a-month contraceptive pill combined with a progesterone since the late 1960s *(28)*. Quinestrol by itself is not biologically active, but, after oral intake, it is stored in fat tissue from where it is slowly released and metabolized to ethinylestradiol – it has a long half-life. The progestogen component is short-acting and produces a progestogen peak followed by a decline which induces a menstruation-like withdrawal bleeding, typically starting on day three after intake of the pill *(28, 29)*.

Quinestrol has historically been combined with quingestanol, norgestrel or levonorgestrel. Quingestanol acetate, the 3-cyclopentylenol ether derivative of norethindrone acetate, is a progestin with twice the potency of and with the same biological profile as norethindrone acetate *(30)*. In 1969, three contraceptive pill

formulations were introduced in China: the three preparations contained 3.0–3.3 mg quinestrol and a progestogen (norgestrel 12 mg, chlormadinone 15 mg or 16-methylene-chlormadinone 10 mg) *(31)*. Since 1998, a pill containing quinestrol 3.0 mg and LNG 6 mg has been the only quinestrol-containing pill that has received approval for use in public clinics in China *(32)*. Pills containing quinestrol 3.0 mg and norgestrel 12 mg have also been reported to be available in such clinics *(33)*.

The GDG examined the following key question: "Should quinestrol-containing pills be added to the contraceptive method mix for women of reproductive age, including Quin-Quin, Quin-LNG and Quin-NG?"

3.3.2 Balancing desirable and undesirable effects

Evidence from one RCT *(34)* and 11 case series *(30, 35–44)* was included, with searches updated to 1 December 2024. The RCT included 732 participants under 40 years of age. One group (n = 370) received 3 mg quinestrol, combined with 6 mg LNG (Quin-LNG), with a total follow-up period of 6560 cycles and a control group (n = 362) received 3 mg quinestrol, combined with 12 mg norgestrel (Quin-NG), with a total of 5716 follow-up cycles. The 11 case series (4632 participants) focused on quinestrol combined with quingestanol (Quin-Quin). There was very low-certainty evidence for all the effects.

In terms of efficacy, 10 pregnancies occurred in 370 participants (2.7%) in the Quin-LNG group and 14 pregnancies among 362 participants (3.87%) in the Quin-NG group. Compared with Quin-NG, Quin-LNG may result in 12 fewer pregnancies per 1000 women, ranging from 21 fewer to 21 more (RR 0.70, 95% CI: 0.31 to 1.55). Among the 4093 women using Quin-Quin presented in the 11 case series, 154 pregnancies occurred (3.76%).

According to case series reports of Quin-Quin use, two cases of venous thromboembolism (VTE) (0.12%) occurred among 1684 women taking Quin-Quin. Among the 18 women who experienced a contraceptive failure, no fetal malformations and/or birth defects were reported. There were no reports of breast cancer within the case series (n = 600 Quin-Quin users) recording this outcome. Relevant adverse event outcome data for Quin-LNG and Quin-NG are lacking.

In general, reports of side effects among women participating in the RCT who were assigned to use either Quin-LNG or Quin-NG were similar. Nausea/cramping/vomiting (7.3% vs 11.3%), dizziness (3.7% vs 4.7%) and leucorrhoea (6.4% vs 8.3%) were the most commonly observed side effects, respectively. Reports of side effects were greater among Quin-Quin users compared with women using Quin-LNG or Quin-NG. Nearly 60% of Quin-Quin users experienced dizziness (58.8%), while 35.4% reported headaches, 50.3% noted leucorrhoea and 44% reported vomiting.

During the discussions, the WHO Secretariat informed the GDG that it had received concerns about serious adverse events reported in the media from five countries (e.g. Uganda reported a maternal death, Zambia reported an incidence of venous thromboembolism (VTE), and a bleeding disorder was also reported). The WHO Secretariat indicated that it is unclear what type of quinestrol contraceptive is being taken or when and how often. The GDG suspected that people could be taking quinestrol-containing pills at higher doses and/or more than once per month, which may explain adverse events from high estrogen intake.

3.3.3 Other considerations

Quin-LNG remains commercially available and is associated with relatively low economic costs to the individual; it has been available for over 40 years. Quin-NG is not available to purchase and does not appear to be available online. The GDG noted that many individuals may prefer to have a single monthly oral contraceptive pill, but if unavailable, individuals would find other contraceptives acceptable.

3.3.4 Justification

The GDG made strong recommendations against the inclusion of both Quin-Quin and Quin-NG in the method mix for women of reproductive age. The GDG made a conditional recommendation suggesting against the inclusion of Quin-LNG in the method mix for women of reproductive age. Overall, the GDG judged that there may be serious adverse events with the use of Quin-NG and Quin-Quin and there are uncertain effects on benefits (e.g. risk of pregnancy). For Quin-LNG, the adverse effects are unknown and the effects on benefits are also uncertain (e.g. risk of pregnancy). The evidence overall for benefits and harms was very low, but the potential for harms with Quin-NG and Quin-Quin led the GDG to make a strong recommendation against those formulations. In addition, warnings are needed about the dangers of taking medicines that have not been prescribed for oneself. The GDG agreed that if quinestrol-containing contraceptives were not added to the method mix, there was unlikely to be an important impact on equity. The GDG however noted that more research into an oral contraceptive pill taken once monthly is needed.

3.3.5 Implementation considerations

Owing to reports of serious adverse events linked with quinestrol-containing pill use from news media outlets outside of the health sector in five WHO Member States, the GDG strongly encourages Member States to conduct pharmacovigilance that includes monitoring for adverse events with quinestrol-containing contraceptive pill use. Such pharmacovigilance is particularly warranted because these reported adverse events linked to unregulated use of quinestrol-containing contraceptive pills cannot be confirmed.

3.4 Continuous or extended use of COCs

WHO suggests that COCs can be used for a) extended durations up to six months or b) continuously up to one year, as well as their cyclical use for contraception in women of reproductive age.

Remarks: an extended regimen is defined as taking active combined hormonal contraceptive pills continuously for more than 28 days, followed by a planned hormone-free interval. Extended use may be for fixed[a] or flexible[b] duration up to six months.

A continuous regimen is defined as taking active combined hormonal contraceptive pills every day without any breaks in daily pill-taking (no hormone-free interval) for up to one year.

Conditional recommendation, low-certainty evidence

[a] Fixed: involves taking active hormone pills daily for an extended fixed period of time depending on user preference (e.g. for 60 consecutive days) followed by a 7-day hormone-free interval before restarting the pills.

[b] Flexible: involves taking active pills daily for more than 28 days without a break, but instead of introducing the hormone-free period on a fixed day, the user waits to experience 3–7 consecutive days of breakthrough bleeding or spotting as the cue to introduce a hormone-free period of about 4 days before restarting the pills.

3.4.1 Background

Globally, in 2019, an estimated 151 million women of reproductive age (15–49 years) used COCs or other contraceptive pills for contraception *(45)*, accounting for 14.8% of all contraceptive users *(46)*. First approved in 1960 *(47)*, the contraceptive mechanisms of COCs include: (a) progestins and estrogens suppress the hypothalamus from releasing gonadotropin-releasing hormone, which in turn reduces the release of luteinizing hormone and follicle-stimulating hormone from the pituitary and prevents ovulation *(48, 49)*; (b) progestins thicken cervical mucus and reduce its permeability to sperms *(50, 51)*; and (c) progestins may also reduce endometrial receptivity *(52, 53)*.

The majority of COCs have a 28-day-cycle regimen: 21 active hormone pills followed by 7 days of placebo or no drug, resulting in withdrawal bleeding every 28 days. This regimen was initially designed to accommodate cultural and social pressures rather than address actual biological considerations or contraceptive mechanisms of action *(54)*. Nevertheless, some users find daily pill-taking burdensome and adherence a challenge. As a result, continuous and extended COCs pill-taking regimens have been developed to offer alternatives – without compromising contraceptive efficacy – that may be more attractive to some COCs users (e.g. fewer menstrual cycles, reduced need for feminine hygiene products).

Therefore, the GDG examined the following key question: "Should COCs at extended or continuous duration versus cyclical use be used in women of reproductive age?"

3.4.2 Balancing desirable and undesirable effects

A systematic review was conducted up to October 2024 and found 18 RCTs *(55–72)* and 10 studies *(73–82)* of other study designs.

Evidence of moderate certainty showed that there is likely no difference between use of continuous or extended regimen compared to cyclic use, in terms of unintended pregnancy rates or Pearl Index. There would likely be one fewer unexpected pregnancy per 1000 women in one year with extended or continuous regimens (odds ratio [OR] 0.79, 95% CI: 0.41 to 1.52) and the Pearl Index would likely be 0.20 lower (from -1.31 to 0.92). Results from five studies *(55, 56, 58–60)* consistently demonstrated a favourable effect for continuous or extended-cycle use of COCs on reducing scheduled bleeding and/or spotting but an unfavourable effect on unscheduled bleeding and/or spotting. However, across the studies, their results consistently showed that there will likely be fewer bleeding-only days but more spotting-only days with continuous or extended use of COCs. Additional analyses explored effects with flexible or fixed duration regimens; flexible regimens may result in less bleeding, but the evidence is uncertain.

Regarding harms, low-certainty evidence showed that there may be little to no difference in harms with extended or continuous use of COCs. There may be 45 more women per 1000 women experiencing side effects such as headaches or dysmenorrhoea (OR 1.20, 95% CI: 1.03 to 1.41) and 10 fewer serious adverse events (OR 0.69, 95% CI: 0.27 to 1.73). Six RCTs *(55, 58, 60, 65, 66, 72)* including 4517 women measured deep vein thrombosis (DVT)/VTE over one year. When comparing the continuous or extended use of COCs with cyclic COCs, the odds of developing DVT/VTE is 1.05 with a 95% CI of 0.16 to 6.79, indicating 0.7 more DVT/VTE cases per 1000 women in extended or continuous COCs users than cyclic COCs users. Three longitudinal studies measured the incidence of DVT/VTE in continuous or extended COCs users. In one cohort study *(82)*, three cases of DVT (including one case of postoperative thrombosis) occurred in 727 participants who received the flexible regimen during the overall two-year period. Results from Optum Research Database in the United States of America from January 2006 to June 2017 *(77)* reported a hazard ratio of 1.40 (95% CI: 0.90 to 2.19). According to data from another medical record database, from May 2007 to September 2015 *(78)*, the absolute risk difference and incidence rate difference in VTE was 0.27 per 1000 persons and 0.35 cases per 1000 person-years between the continuous/extended use of COCs and the cyclic COCs users, respectively.

3.4.3 Other considerations.

Moderate-certainty evidence came from eleven RCTs *(55, 56, 58–62, 65, 66, 69, 72)* and three studies of other study designs *(73, 76, 79)* reporting outcomes related to the acceptability of using continuous or extended-cycle COCs. In general, there is likely high satisfaction with continuous or extended-cycle use of COCs, and in most studies higher satisfaction compared to cyclic use. Most studies *(55, 65–67, 70)* showed that there is likely no difference in compliance or discontinuation up to one year between all the regimens. Additional analyses providing low-certainty evidence showed that discontinuation may be due to bleeding, but the numbers of women discontinuing was importantly greater with continuous or extended-cycle COCs, although discontinuation may be higher in regimens with progestin. The GDG agreed that if an individual discontinued the extended or continuous regimen, there would be few barriers to moving to cyclic use, but that women may discontinue because of unexpected bleeding patterns or the belief that women should have a period at certain time points.

The GDG judged that the costs of COCs may be similar between regimens, but there may be slight cost savings to the user with less need for menstrual products. The number of health-care visits is also likely to be similar between regimens, since counselling to explain how to take extended or continuous regimens could occur in those visits. Overall, the cost differences are likely to be negligible. Use of an extended or continuous regimen is probably feasible and there is unlikely to be an impact on equity given the current widespread availability of COCs.

3.4.4 Justification

The GDG made a conditional recommendation suggesting that COCs can be used for extended durations up to six months or continuously up to one year, as well as their cyclical use for contraception in women of reproductive age. Overall, there is moderate-certainty evidence that there are likely to be small differences in the benefits of extended or continuous regimens compared to cyclic use, and the harms (e.g. VTE/DVT) are likely to be similar to cyclical regimens of other contraceptives. The GDG agreed that effects may not vary by duration. Acceptability is probably high, and there may be little difference in discontinuation between regimens. Extended or continuous regimens are probably feasible. The costs may vary in different contexts, but in most countries, the cost differences are likely to be negligible and would not reduce equity. However, counselling for women should be provided to explain how to use these regimens and whether bleeding should occur or be expected.

3.4.5 Implementation considerations

When implementing this recommendation, the GDG underscored the importance of the right to contraceptive choice. Further, the GDG emphasized the imperative of addressing the following overarching issues when adding continuous- or extended-use COCs regimens to national programmes.

- Informed consent
- Elements of quality of care
- Essential screening procedures for administering COCs
- Provider training skills
- Referral and follow-up care for contraceptive use, as appropriate.

In addition, when implementing this recommendation at a programme level, there are important considerations (e.g. additional training for health-care providers, and resources to manage and counsel women about benefits and harms). Specifically, the GDG highlighted that extended or continuous use of COCs needs:

- enhanced counselling (e.g. about changes in bleeding patterns), which may not be practical in some settings; and
- adequate supplies of COCs, which may not exist in all settings.

3.5 Extended use of etonogestrel contraceptive implants

WHO suggests etonogestrel (ETG) contraceptive subdermal implants can be used up to five years, in line with updated manufacturers' approved duration of five years.

Conditional recommendation, very low-certainty evidence

3.5.1 Background

The ETG implant is a single rod of ethylene vinyl acetate copolymer containing 68 mg of ETG, covered in a rate-controlling membrane *(83, 84)*. The ETG implant reliably inhibits ovulation when serum levels remain above 90 pg/ml *(83)*. Although labelled for use up to three years when first approved in 1998, the consistent serum levels observed at the end of the three-year period of use suggested that the implant could continue to provide effective contraception beyond the approved duration. The current WHO SPR describes product labelling regarding length of use for "Implanon NXT (also known as Nexplanon; replaces Implanon) which is a 1 rod containing ETG, labelled for up to 3 years of use" *(2)*. On 16 January 2026, the manufacturer announced an update of the Nexplanon product label, following the United States Food and Drug Administration approval of the use of Nexplanon for pregnancy prevention in women of reproductive potential for up to fiveyears (https://organonpro.com/en-us/product/nexplanon/home/).

Prolonging the use of the ETG implant beyond three years of use could offer substantial benefits including improved accessibility, reduced need for replacements and overall lower health-care costs. This may be especially important in lower-resource settings where regular clinical follow-ups may be more challenging.

Therefore, the GDG examined the following key question: "Should ETG contraceptive subdermal implants be used up to five years versus three years in women of reproductive age?"

3.5.2 Balancing desirable and undesirable effects

A systematic review of studies published up to 8 November 2024 found six studies comparing the extended interval use of ETG implant for contraception beyond three years to the currently approved duration of three years. Two studies (306 participants) assessed efficacy of the implant within three to five years, as measured by Pearl Index or pregnancy rate *(85, 86)*. This evidence was judged to be of low certainty: the Pearl Index was 0/100 woman-years, indicating zero pregnancies were recorded during the observation period. Six studies (860 participants) assessed efficacy of the implant within three to four years according to the Pearl Index *(85–90)*. This evidence was also of low certainty: the Pearl Index ranged from 0 to 1.4/100 woman-years across the studies during this time, with three pregnancies occurring during the first three years of implant use. The GDG discussed whether there could be differences in efficacy based on body mass index (BMI). However, some laboratory evidence suggests that there may be no differences (e.g. serum levels are not lower if BMI is greater).

One study (204 participants) reporting very low-certainty evidence assessed acceptability of the implant within three to five years measured by bothersome bleeding prompting removal *(85)*. The proportion of bothersome bleeding prompting removal during this timeframe was 11/204. Four studies (494 participants) presenting low-certainty evidence assessed acceptability of the implant within three to four years measured by bothersome bleeding

prompting removal *(85, 88–90)*. Across these four studies, the proportion of bothersome bleeding prompting removal during this time was 15/494.

3.5.3 Other considerations

There was very low-certainty evidence for acceptability of the implant within three to five years; there were 11/204 removals beyond the currently approved duration of three years *(84)*. At three to four years, there was low-certainty evidence from four studies (494 participants) which reported 15 removals *(85, 88–90)*.

The GDG agreed that extending the use of the implant could lead to a reduction in overall number of procedures and visits for women, as well as a reduction in overall cost to the medical system and to the patient. Outside of education and guideline changes, no significant infrastructure changes are needed to support a duration longer than three years given that the contraceptive method would already be in place. There was some concern that clinicians may not offer replacement at three years if extended use was available; information should be provided to enable women to make their own decision about length of use of the implant. The GDG also indicated that there could be some confusion that women who do not remove it may think that they can become pregnant after the three years. However, the GDG agreed that providing education and information could reduce any misconceptions.

3.5.4 Justification

The GDG made a conditional recommendation suggesting that ETG contraceptive subdermal implants can be used for up to five years. There was very low-certainty evidence that extended use of ETG contraceptive implants up to five years may be as effective and safe as implants up to three years. The longer duration is probably acceptable to women and clinicians and would have little impact on equity but could reduce the need for resources associated with visits, procedures and costs. Implants up to five years are probably as feasible to provide as up to three years and would not require additional implementation strategies.

3.5.5 Implementation considerations

When implementing this recommendation, the GDG underscored the paramount importance of the right to contraceptive choice. The GDG emphasized the imperative of addressing the following overarching issues when adding extended use of ETG implants to national programmes.

- Informed consent
- Elements of quality of care
- Essential screening procedures for administering ETG implants
- Provider training skills
- Referral and follow-up care for contraceptive use, as appropriate.

The GDG advised that WHO Member States should specifically consider the following when implementing extended use of ETG implants.

- A client's right to contraceptive choice and how long they wish to use an implant must be protected.
- Allowing for extended use may require additional national-level policy and programmatic decisions depending on the national regulatory and legal context.
- Irrespective of the option to extend implant use, programmes and providers must safeguard a client's right to have their implant removed when they wish.
- Additional training and communication materials may be needed for providers to implement extended implant use.

Lastly, the GDG encourages WHO Member States to continue to enable access to implant removals, as well as opportunities to train clinicians to remove implants.

4 Guideline-relevant research needs

As part of its deliberations and considerations, the GDG identified an array of knowledge gaps related to recommendations within the ECO guideline, where further research could strengthen the existing body of evidence and contribute to potential improvements in expanding contraceptive method choices and client-centred contraceptive services. While recognizing the topics are neither complete nor exhaustive, the GDG aims to stimulate researchers and institutions supporting research on contraception to pursue these topics within their research portfolios.

Generally, and across all methods discussed, the GDG noted that where there is low- or very-low-certainty evidence for priority outcomes (such as pregnancy and serious adverse effects including VTE), additional high-quality studies are needed. While RCTs comparing different contraceptives, doses, duration or formulation would be ideal, large prospective studies and/or pharmacovigilance could also provide high-quality evidence. In addition, acceptability studies of different contraceptive methods should also be undertaken to inform education and counselling efforts. The following sections highlight research gaps specific to the contraceptive method.

4.1 Mifepristone for EC

The GDG identified that additional research should be conducted on the effects of mifepristone on breastfeeding and breast milk. Particular to mifepristone are questions related to the optimal dose for EC, the timing (e.g. within five days), understanding the effect of repeated use within a menstrual cycle and if effects vary by subgroups (e.g. people with high BMI where there is the potential for alterations in pharmacokinetics). The GDG also noted that research is needed to determine the effects of mifepristone as an emergency contraceptive following a medical abortion regimen (e.g. when a higher dose of mifepristone has been used), and when hormonal contraceptives (e.g. implants or switching) should be started after using mifepristone as an emergency contraceptive. Implementation and acceptability research, in particular related to barriers to access and cultural context, could inform policy and programmes, especially in settings where it is not currently used.

4.2 Ormeloxifene

As well as the need for high-quality research for efficacy and safety, the GDG highlighted the need for research into the effects of ormeloxifene on breastfeeding (breast milk) and neonatal health, and long-term outcomes such as osteoporosis (bone mineral density), BMI, cardiovascular outcomes, urinary incontinence and uterine prolapse. One of the perceived benefits of ormeloxifene is the infrequent dosing schedule, and therefore additional research on the effects of dosing schedules on compliance and efficacy could inform future development of contraceptive methods.

4.3 Quinestrol-containing pills: Quin-Quin, Quin-LNG and Quin-NG

Given the concerns with Quin-Quin and Quin-NG, the GDG emphasized the need to collect data related to adverse events across multiple platforms (including pharmacovigilance and social media). The GDG also noted that, in general, research into reversible oral contraceptive methods with monthly dosing should be conducted.

4.4 Continuous or extended use of COCs

Although there was moderate-certainty evidence for the effects of extended or continuous use compared to cyclic use of COCs for most outcomes, there remained uncertainty for the effects on bleeding, especially in relation to progestin content of different COCs formulations, and on return to fertility. Most studies followed women up to one year, and therefore studies reporting longer-term use would be valuable.

4.5 Extended use of ETG contraceptive implants

The evidence for extended use of ETG contraceptive implants beyond three years was of very low certainty for some outcomes, and there was no evidence for other critical outcomes. Therefore, additional research is needed in general, but should also measure bleeding patterns, drug-drug interactions and removal complications. While data are needed for all women, the GDG questioned whether high BMI could reduce the effects of the implants beyond three years. Finally, the GDG encouraged research into possible toxicity of continued use of ETG implants, especially in women who have a new implant inserted immediately after the removal of the old one.

5 Publication, dissemination, monitoring and evaluation

The WHO ECO guideline is published in English on the WHO website (iris.who.int). Translations into the six official United Nations languages will be undertaken in collaboration with WHO regional offices. When available, these translations will be accessible through the WHO/HRP webpage at http://www.who.int/hrp.

A comprehensive dissemination and evaluation plan will be designed and implemented. This plan will include widespread dissemination through the WHO regional and country offices, WHO Member States, WHO collaborating centres, professional organizations (e.g. International Federation of Gynecology and Obstetrics and International Confederation of Midwives), governmental and nongovernmental partner organizations working in sexual and reproductive health, and civil society groups engaged in sexual and reproductive health projects. HRP and WHO communications will create awareness about the guideline through various media platforms.

A strategic launch event will be organized to coincide with important sexual and reproductive health conferences. WHO will collaborate with its regional offices to organize webinars for stakeholders in English and other United Nations languages. The systematic reviews which informed the guideline's recommendations will be published in peer-reviewed journals.

After the guideline's dissemination, an evaluation survey targeting ministries of health, WHO offices and partners, professional organizations and civil society will be undertaken to assess the extent and effectiveness of the dissemination, evaluate the level of inclusion of these methods in national family planning programme method mixes and identify barriers to effective implementation. In collaboration with its Member States and partners, WHO will monitor the implementation and impact of the recommendations at the health-service, national and regional levels.

6 Updating

At a minimum, this guideline will be reviewed every five years. In the interim, WHO will continue to monitor the body of evidence informing these recommendations using the Continuous Identification of Research Evidence process (CIRE) *(91)*. The CIRE system was created by WHO and its partners in 2002 to identify regularly and systematically, newly published evidence that is relevant to WHO family planning guidelines. To this end, WHO will convene additional consultations, as needed, should new evidence around the methods in this guideline be identified through the CIRE process, or should new contraceptive methods and service delivery practices become available and utilized within WHO Member States. This may entail the updating of evidence regarding existing methods in the guideline and any changes in the recommendations, the addition of new emerging methods to the guideline and the transitioning of methods from this guideline to the WHO MEC, and new service delivery practices to the SPR once they meet the necessary criteria. Any change in recommendation will be promptly communicated to Member States and partners to guide policy and programming.

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Annexes

Annex 1 Declarations of interests from Guideline Development Group members

Of the 20 experts who participated in this work, six declared an interest related to contraception (see details below in alphabetical order). The World Health Organization (WHO) Secretariat reviewed all declarations and determined that Beena Joshi reported a potentially significant conflict of interest related to the topic of ormeloxifene which precluded her from participating in the discussion and recommendation development related to ormeloxifene. Declarations of conflicts of interest from the other five GDG members were deemed insignificant in view of the topics being discussed in the GDG meeting, consequently, they were invited to fully participate in the WHO *expanding contraceptive options (ECO)* GDG meeting.

A1.1 Individuals without any conflict or with non-significant conflicts of interest

Andy Gray was a member of the South African National Essential Medicines List Committee (until April 2025). This committee is responsible for medicines selection and the development of standard treatment guidelines in the public sector. He serves on three technical advisory committees at the South African Health Products Regulatory Authority. He is the Chair of the Names and Scheduling Committee, a member of the Pharmacovigilance Committee and a member of the Legal Committee. He has not received any income or honorarium from these activities.

Lisa Haddad is employed by the Population Council, where her work involves developing novel contraceptive methods.

Philip Hannaford serves as the Chair of the United Kingdom's Commission on Human Medicines, Medicines for Women's Health Expert Advisory Group (2020–to date). He has been a member of this Advisory Group since 2011. In this capacity, he provides expert opinion on regulatory matters in relation to contraceptives. The fee is approximately £ 250 for each meeting attended.

Beena Joshi is an employee of the Indian Council for Medical Research (ICMR). ICMR is an organization within the Department of Health Research, Ministry of Health and Family Welfare, Government of India. Ormeloxifene (centchroman) is approved for use in the national family planning programme by the Government of India. ICMR supported the conduct of several of the studies included in the systematic review of the safety and efficacy of ormeloxifene.

Enriquito Lu was the Technical Unit Director for Jhpiego's global portfolio of projects supporting ministries of health to implement high-quality family planning/reproductive health services in compliance with global family planning practices until February 2021. As of February 2021, he has worked for Jhpiego on a part-time basis with the family planning/reproductive health unit as a Senior Advisor in supporting initiatives on comprehensive family planning within the Asia Pacific Economic Cooperation (APEC). Lu was a member of the Organizing and Steering committee, as well as a scientific session lead, for the 6th International IUD Symposium that was convened by a consortium of organizations (Columbia University, Population Council, FHI360 and the United States National Institutes of Health; 2020–2021). He received a US$ 1000 honorarium for this role. The engagement was completed in July 2022. He was also a member of the Organizing and Steering Group for virtual courses that provide technical updates on reproductive health services for the International Planned Parenthood Federation's South Asia Regional Office's Member Association clinicians and programme managers. For this role, he

received an honorarium of US$ 1000. This work ended in 2021.

Farida Shah undertook a short-term consultancy related to reproductive, maternal, newborn, child and adolescent health with the WHO Country Office, Somalia. The consultancy ended in July 2022.

The following GDG members had no conflicts of interest declared, and internet searches and public scrutiny did not reveal any undeclared conflicts of interest. They therefore participated in the GDG meetings fully, including discussions, decision-making and voting on recommendations: Faisal Abbas, Valeria Bahamondes, Harriet Chanza, Rodica Comendant, Katherine Curtis, Galina Dikke, Unnop Jaisamrarn, Philip Mbithi Muia, Ashraf Nabhan, Ingrid Sääv, Aparna Sridhar, Nandana Suresh, Kun Tang and Peace Samuel Umanah.

A1.2 Expertise of GDG members

Faisal Abbas: health economics; population studies; gender and development

Valeria Bahamondes: women's health research; clinical trials; medical monitor and safety pharmacovigilance

Harriet Chanza: community stakeholder; reproductive health rights; reproductive health management

Rodica Comendant: obstetrics and gynaecology; training and capacity-building

Katherine Curtis: epidemiology; evidence synthesis; guideline development

Galina Dikke: abortion care; obstetrics and gynaecology; training

Andy Gray: pharmacology; pharmaceutical policy; IT-based health-care solutions; pharmacovigilance; essential medicines; scientific editing; development and assessment of medicines; guideline development

Lisa Haddad: obstetrics and gynaecology; novel contraception research; product development

Philip Hannaford: clinical practice; epidemiology; women's health; primary care; research and knowledge exchange; pharmacovigilance

Unnop Jaisamrarn: women's health; clinical trials

Enriquito Lu: research and innovation; guideline and training curricula development; smart technologies; programme management

Philip Mbithi Muia: sexual and reproductive health and rights; human rights; gender and diversity; equity and social inclusion

Ashraf Nabhan: obstetrics and gynaecology; research; evidence synthesis; guideline development

Ingrid Sääv: obstetrics and gynaecology; abortion care; contraceptive devices

Farida Shah: nursing and midwifery; community health nursing; health economics; health workforce planning and management; quality improvement; programme development and management; primary health care; humanitarian settings

Aparna Sridhar: adolescent sexual and reproductive health; innovation; obstetrics and gynaecology

Nandana Suresh: user perspectives; office management and administrative support

Kun Tang: epidemiology; sexual and reproductive health and rights; development aid research

Peace Samuel Umanah: youth perspectives; communications; advocacy

Annex 2 Evidence-to-decision tables

A2.1 Recommendation: mifepristone for emergency contraception

Should mifepristone be recommended for inclusion in the contraceptive method mix for emergency contraception (EC) or not?	
Population	Women of reproductive age
Intervention	Mifepristone for EC
Comparison	Other emergency contraceptives
Main outcomes	Contraceptive efficacy: pregnancy rate or proportion; ectopic pregnancy and pregnancy outcomes if fails (including live birth, termination, miscarriage); side effects: early/delayed menses, abnormal uterine bleeding, cramping or pain, gastrointestinal symptoms, others Acceptability (satisfaction), resources/costs, feasibility, equity
Setting	Outpatient
Perspective	Population
Background	Emergency contraceptive oral methods are currently used and include ulipristal acetate, levonorgestrel (LNG), combined oral contraceptives (COCs) – often referred to as the Yuzpe method – and the copper intrauterine device (IUD). Globally, many of these methods remain inaccessible to many people due to lack of resources. Mifepristone is a norethindrone derivative that strongly binds to progesterone and glucocorticoid receptors, functioning as an antagonist. Mifepristone has been found to delay or prevent ovulation via this progesterone receptor antagonism. Mifepristone is widely used for medical abortion. It is used in a few countries around the world as EC, including Armenia, China, the Russian Federation and Ukraine.
Conflicts of interest	None

Assessment

Desirable effects
How substantial are the desirable anticipated effects?

Judgement

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

A systematic review of studies up to December 2024 found 86 randomized controlled trials (RCTs) comparing mifepristone to other methods of EC (COCs [Yuzpe method], LNG oral pills and copper IUDs). Most studies took place in China *(1)*.

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk within other method	Risk difference with mifepristone
				LNG	**Risk with mifepristone**
Risk of pregnancy (mid-dose 25–50 mg mifepristone)	6052 (27 RCTs)	⨁⨁⨁◯ Moderate	RR 0.67 (0.49 to 0.91)	30 per 1000	**12 fewer per 1000 (3 to 18 fewer)**
Risk of pregnancy (low-dose < 25 mg mifepristone)	8752 (14 RCTs)	⨁⨁⨁⨁ High	RR 0.73 (0.59 to 0.90)	30 per 1000	**5 fewer per 1000 (2 to 8 fewer)**
				YUZPE	
Risk of pregnancy	2144 (3 RCTs)	⨁⨁⨁◯ Moderate	RR 0.14 (0.05 to 0.41)	25 per 1000	**22 fewer per 1000 (15 to 24 fewer)**
				Copper IUD	
Risk of pregnancy	395 (2 RCTs)	⨁◯◯◯ Very Low	–	There were 3/245 pregnancies with mifepristone; and 0/150 with copper IUD (12 more per 1000 with mifepristone)	

CI: confidence interval; GRADE: Grading, Recommendations, Assessment, Development and Evaluation; IUD: intrauterine device; LNG: levonorgestrel; RCT: randomized controlled trials; RR: risk ratio.

Additional considerations

Studies directly comparing mid-dose to low-dose mifepristone also found fewer pregnancies with mid-dose mifepristone, but the difference is very small (trivial). The Guideline Development Group (GDG) agreed that effects are seen with lower doses.

The GDG considered that the body mass index (BMI) is likely lower in Chinese participants, however they agreed that evidence would be applicable. The GDG also noted that although results indicated more pregnancies with mifepristone than the copper IUD, the increase is very small and the evidence is uncertain.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

From the same systematic review *(1)*.

Side effects per 1000 women

	Outcomes (risk difference)						
	Ectopic pregnancies	Any side effect	Nausea	Vomiting	Spotting/ bleeding	Altered menses	
						Early	Delayed
Mid-dose vs LNG	–	91 fewer (48 to 123 fewer) Moderate	15 fewer (35 fewer to 14 more) Low	–	96 fewer (77 to 113 fewer) Moderate	27 fewer (48 fewer to 3 more) Moderate	31 more (1 to 68 more) Moderate
Low-dose vs LNG	1 fewer Moderate	253 fewer (212 to 284 fewer) Moderate	5 fewer (21 fewer to 12 more) Moderate	3 more (3 fewer to 11 more) Moderate	115 fewer (95 to 135 fewer) High	100 fewer (76 to 118 fewer) High	35 more (7 to 72 more) High
Mifepristone vs Yuzpe	–	78 fewer (35 to 120 fewer) Moderate	152 fewer (119 to 182 fewer) High	120 fewer (109 to 126 fewer) High	–	–	202 more (145 to 273 more) High
Mifepristone vs copper IUD	–	–	–	–	–	–	138 more (24 to 450 more) Very low
Mid-dose vs low-dose	1 more Low	40 more (4 to 93 more) Moderate	9 more (10 fewer to 33 more) High	6 more (2 fewer to 28 more) High	47 more (13 to 97 more) High	13 more (5 fewer to 33 more) Low	38 more (17 to 59 more) High

LNG: levonorgestrel; IUD: intrauterine device.

Additional considerations

The GDG agreed that the side effects are trivial and are also tolerable. There may be slightly fewer side effects with lower doses, although even in other conditions where mifepristone is used daily and in higher doses it has been found to be safe.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence and additional considerations
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Although most studies were from China, results are applicable to other settings. Sensitivity analyses were conducted according to risk of bias, but effects were maintained with or without studies at high risk of bias – so evidence was not rated down for risk of bias. For most side effects, the evidence was high or moderate. Therefore, the overall evidence was moderate.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence and additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The GDG agreed that most women would probably place higher value on avoiding pregnancy.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence and additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	There are likely trivial differences in benefits and harms between mifepristone and other emergency contraceptive methods.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence and additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. Additional considerations Estimates for cost for mifepristone was found in different countries. • The Russian Federation: ~US$ 8/€ 7 (Zhenale 10 mg) • Moldova: ~US$ 5 /€ 4.3 (Ginestril 10 mg – no longer made) • Global average LNG: ~US$ 11–40/€ 9.5–34 • Global average Yuzpe: (~US$ 0.25–15/€ 0.2–13 outside the United States of America [USA]) • For 10 mg US$ 0.60–0.70 (in practice – significantly lower cost than LNG) • For 25 mg US$ 0.90–1.00 • For 50 mg or more US$ 1.20–1.35

Equity
What would be the impact on health equity?

Judgement	Research evidence and additional considerations
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence found. The GDG agreed that given the lower costs it may increase equity. However, it may not be available in many countries.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence and additional considerations					
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Anticipated absolute effects (95% CI)		Risk difference (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with mifepristone	Risk with Comparator				
	(Mid- and low-doses)	LNG or Yuzpe	77 more per 1000 (51 to 95 more)	RR 1.09 (1.06 to 1.11)	1339 (2 RCTs)	⨁⨁⨁◯ Moderate
	938 per 1000 (912 to 956)	861 per 1000				Rated down for risk of bias because of high loss to follow-up

CI: confidence interval; GRADE: Grading, Recommendations, Assessment, Development and Evaluation; LNG: levonorgestrel; RCT: randomized controlled trial; RR: risk ratio.

Additional considerations

The GDG agreed that there may be some concerns related to potential for misuse, however these could be overcome by education, packaging or promotion.

Feasibility
Is the intervention feasible to implement?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The GDG discussed that it would be important that there is quality assurance for its use. There may need to be planning in countries to determine how it is made available (e.g. over the counter or prescribed) and whether the costs are covered.

Summary of judgements

	Judgement						
Desirable effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

Conclusions

Recommendation

WHO recommends adding mifepristone to the method mix for EC, as a single dose between 10 and 50 mg (strong recommendation, moderate certainty of evidence)

***Remarks*: the availability of mifepristone dosage forms may differ across setting and countries. A dose between 10 and 25 mg may be preferred if available. EC pills are taken as soon as possible after unprotected sex and within five days.**

Justification

Overall, there is moderate-certainty evidence that mifepristone is likely as effective and safe as other emergency contraceptive methods. Providing it instead of other methods would likely result in moderate cost savings given its lower costs and increase equitable access to EC if made widely available and if the cost is covered. It is probably as acceptable to women and clinicians as other methods, and probably feasible to provide. There is some concern that education and literature will be necessary to ensure quality assurance and appropriate use.

Implementation considerations

Consideration of the cost of mifepristone dosages within a country will be important to implement this recommendation. The GDG notes the cost of mifepristone dosages may vary depending upon the country: current estimates range from US$ 0.90–1.00 for 25 mg and US$ 1.20–1.35 for 50 mg.

A2.2 Recommendation: ormeloxifene

Should WHO recommend adding ormeloxifene to the contraceptive method mix for women of reproductive age?	
Population	Women of reproductive age
Intervention	Ormeloxifene
Comparison	Other contraceptives or none
Main outcomes	Number of pregnancies; Pearl Index; bleeding; amenorrhoea; side effects (e.g. headaches, nausea); serious adverse events (e.g. thrombosis, fetal birth defects if contraception fails) Acceptability, resources/costs, feasibility, equity
Setting	Outpatient
Perspective	Population
Background	Ormeloxifene is a non-steroidal selective estrogen receptor modulator that acts on estrogen receptors selectively. It is commonly used as a 30 mg tablet taken twice weekly for 12 weeks, then once weekly. It modulates the body's response to estrogen. Common indications for use of ormeloxifene include contraception, abnormal uterine bleeding, fibrocystic breast disease and prevention of osteoporosis. It has been available in the Indian market since1992 and only approved in India. It is on the National List of Essential Medicines 2022 of India, but it is not on the WHO Essential Medicines List. It is very low cost (or free in India) and is taken by approximately 2 million women.
Conflicts of interest	None

Assessment

Desirable effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence and additional considerations
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	A systematic review was conducted up to December 2024 and found 13 studies *(2)*: • one RCT comparing ormeloxifene to COCs (n = 240) • one non-randomized study comparing ormeloxifene to COCs (n = 200) • one RCT comparing ormeloxifene to postpartum intrauterine contraceptive device • 10 case series (n = ~5300).

Pregnancies

Participants (studies)	Certainty of evidence	Study event (%)		Relative effect (95% CI)	Anticipated absolute effects	
		With COCs	With ormeloxifene		Risk with COCs	Risk difference with ormeloxifene
383 (2 comparative studies)	⨁⨁⨁◯ Very low	3/173 (1.7%)	2/210 (0.95%)	RR 0.55 (0.09 to 3.25)	17 per 1000	8 fewer per 1000 (from 16 fewer to 39 more)

CI: confidence interval; COCs: combined oral contraceptives.

Pearl Index

Participants (studies)	Overall certainty of evidence	Absolute effect (Pearl Index)	Note
5985 receiving ormeloxifene (8 case series, 2 RCTs, 1 observational comparative study)	⨁⨁⨁◯ Very low	0.48–4.2 pregnancies per 100 woman-years with ormeloxifene	Method failure: 0–4% across the 10 studies User-related failure: 0.8–10.1% across the studies

RCT: randomized controlled trial.

Reversibility (pregnancy in people who stopped taking ormeloxifene)

One study reported that 21 out of 22 women became pregnant in 6–12 months (very low-certainty evidence).

Additional considerations

The GDG agreed that the number of pregnancies with ormeloxifene is similar to the percentages with other contraceptives, which usually ranges from 4 to 7% for typical use, and was similar in the comparative studies.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence and additional considerations
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	From the same systematic review. • None of the 13 studies reported venous thromboembolism (VTE), hypertension, endometrial hyperplasia, hepatotoxicity, uterine prolapse, urinary incontinence, vaginal dryness, bone mineral density changes, breastfeeding performance and safety for newborns, and heavy vaginal bleeding (very low-certainty evidence). • It was unclear whether it was measured, and none occurred or it was not measured and therefore not reported.

Side effects

Number of participants	Abnormal uterine bleeding	Headache	Weight gain	Nausea/ vomiting	Discontinue due to menstrual irregularity
Ormeloxifene = 90 COCs = 53	Irregular cycle: I = 11.1% C = 7.5% Breakthrough bleeding: I = 0 C = 11.3%	I = 1.1% C = 7.5%	I = 0 C = 13.2%	I = 1.1% C = 9.4%	I = 11.1% C = 7.5%
Ormeloxifene = 120 COCs = 120	Delayed cycle: I = 19.2% C = 5.8% Light flow: I = 22.2% C = 7.77% Amenorrhoea: I = 3.3% C = 0	–	–	I = 3 months (1.66%), 6 months (0), 12 months (0) C = 3 months (8.84%), 6 months (14.81%), 12 months (3.73%)	I = 4% C = 3.33%

COCs: combined oral contraceptives.
I = ormeloxifene; C = COCs.

Additional considerations

The side effects were inconsistent between the two comparative studies, and the evidence was uncertain about whether there were no adverse events.

The GDG discussed whether studies including women with other conditions (e.g. postmenopausal women) receiving ormeloxifene could be included to provide evidence for undesirable effects. The GDG agreed not to include these studies as the population would be too indirect to inform these outcomes (e.g. differences in hormonal levels may affect adverse effects).

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence and additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There was very low-certainty evidence from the studies due to concerns with risk of bias and very little comparative data. In addition, there was also some concern that all studies were conducted in India in people who were attending government clinics.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence and additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The GDG agreed that most women would probably place higher value on avoiding pregnancy.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence and additional considerations
○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Given that the benefits and the harms may be similar between ormeloxifene and other contraceptives (although uncertain), the balance probably does not favour either.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence and additional considerations
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. Additional considerations The GDG noted that ormeloxifene is very low cost in India or may be covered at no cost to the patient.

Equity
What would be the impact on health equity?

Judgement	Research evidence and additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence found. Additional considerations The GDG identified that ormeloxifene is currently distributed mostly in the public sector through government clinics, but there is some effort to increase availability.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There were four studies from the systematic review that measured satisfaction or acceptability. From the two comparative studies, satisfaction was slightly higher with ormeloxifene (78 vs 65%, n = 240; and 45 vs 41%, n = 143). In two studies where satisfaction was measured in people taking ormeloxifene only, satisfaction was approximately 75% and ranging from 96% to 83% over time from one to six months.

Feasibility Is the intervention feasible to implement?	
Judgement	**Research evidence and additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Ormeloxifene needs to be taken only once weekly, making it feasible. It also appears feasible to distribute as its use has increased over time in India and is now used by very large numbers of people (around 2 million).

Summary of judgements

	Judgement						
Desirable effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	**Don't know**
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

Conclusions

Recommendation

WHO suggests against adding ormeloxifene to the contraceptive method mix for women of reproductive age.

***Remarks*: high-quality evidence of the efficacy and safety of ormeloxifene as an oral contraceptive is needed.**

Justification

Overall, the GDG determined that the evidence for ormeloxifene suggests that its effect on the prevention of pregnancy and side effects associated with its use are similar to other COCs, but the evidence is uncertain. The effect on adverse events is unknown due to the very low quality of reporting and presentation of the safety data. The GDG judged the inability to assess adverse events to be of major concern. The GDG determined that the seriousness of this concern warrants suggesting against the inclusion of ormeloxifene into a national contraceptive method mix until high-quality evidence on its safety becomes available. The cost of ormeloxifene is very low (and currently can be covered) in India which may increase equitable access to contraceptives, and evidence suggests that it is acceptable to individuals and feasible given the once weekly dosage schedule. Since the effects on benefits and harms (including adverse events) are uncertain, a conditional recommendation not to add it to the contraceptive method mix was made.

Implementation considerations

The GDG did not discuss implementation considerations for this recommendation.

A2.3 Recommendation: quinestrol-containing pills: quinestrol-quingestanol, quinestrol-levonorgestrel and quinestrol-norgestrel

Should WHO recommend adding to the contraceptive method mix for women of reproductive age?	
Population	Women of reproductive age
Intervention	Quinestrol-containing pills (quinestrol-quingestanol [Quin-Quin], quinestrol-levonorgestrel [Quin-LNG], quinestrol-norgestrel [Quin-NG])
Comparison	Other contraceptives or none
Main outcomes	Number of pregnancies; Pearl Index; bleeding; amenorrhoea; side effects (e.g. headaches, nausea); serious adverse events (e.g. thrombosis, fetal birth defects if contraception fails) Acceptability, resources/costs, feasibility, equity
Setting	Outpatient
Perspective	Population
Background	Quinestrol is a 3-cyclopentylether of ethinylestradiol that has been available in a once-a-month contraceptive pill combined with a progesterone since the late 1960s. Since 1998, a pill containing quinestrol 3.0 mg and LNG 6 mg has been the only quinestrol-containing pill that has received approval for use in public clinics in China. Several countries have banned its use due to concerns around severe adverse events. However, the drug is still sold on the black market in some countries due to its single monthly dosage, which is attractive to users.
Conflicts of interest	None

Assessment

Desirable effects
How substantial are the desirable anticipated effects?

Judgement	Research evidence and additional considerations
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	A systematic review was conducted up to December 2024 and found one RCT and 11 case series that were published between 1970 and 1990 *(3)*.

Outcomes	Quin 3 mg + LNG 6 mg	Quin 3 mg + NG 12 mg	Quin + Quin
Pregnancy events (%)	10/370 (2.70%)	14/362 (3.87%)	154/4093 (3.76%)

LNG: levonorgestrel; NG: norgestrel; Quin: quinestrol: Quin + Quin: quinestrol + quingestanol.

Additional considerations

The GDG agreed that these numbers of pregnancies are similar to the typical percentages with other contraceptives, which usually ranges from 4 to 7% for typical use.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence and additional considerations
● Large for QUIN+NG and QUIN+QUIN ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know for QUIN+LNG	**Safety**

Quin 3 mg + LNG 6 mg	Quin 3 mg + NG 12 mg	Quin + Quin
Venous thromboembolism (participants)		
Not reported	Not reported	2/1684 (0.12%)
Fetal malformations/birth defects (participants)		
Not reported	Not reported	0/18 (0.00%)
Breast cancer (participants)		
Not reported	Not reported	0/600 (0.00%)
Hypertension (participants)		
Not reported	Not reported	2/666 (0.30%) (3130 woman months)

LNG: levonorgestrel; NG: norgestrel; Quin: quinestrol; Quin + Quin: quinestrol + quingestanol.

Additional considerations

WHO described concerns that there have been serious adverse events reported in the media and by five countries (e.g. Uganda reported a maternal death, Zambia reported venous thromboembolism, and a bleeding disorder was also reported). However, a member of the GDG reported that from a large database in Sweden, serious adverse events have not been reported. WHO indicated that it is unclear what type of QUIN contraceptive is being taken or when and how often. The GDG suspected that people could be taking higher doses and/or more than once per month, which may explain adverse events from high estrogen intake.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence and additional considerations		
	Side effects		
	Quin 3 mg + LNG 6 mg	**Quin 3 mg + NG 12 mg**	**Quin + Quin**
	Nausea and vomiting (participants/cycles)		
	Cycles: 476/6560 (7.26%)	Cycles: 647/5716 (11.32%)	Participants: 101/666 (15.17%)
	Nausea (participants/cycles)		
	Not reported	Not reported	Participants: 227/509 (44.60%) Cycles: 1177/28 676 (4.10%)
	Vomiting (participants/cycles)		
	Not reported	Not reported	Participants: 93/509 (18.27%) Cycles: 449/15 859 (2.83%)
	Dizziness (participants/cycles)		
	Cycles: 242/6560 (3.69%)	Cycles: 269/5716 (4.71%)	Participants: 55/94 (58.51%) Cycles: 447/10 055 (4.45%)
	Mood change (cycles)		
	49/6560 (0.75%)	12/5716 (0.21%)	95/5668 (1.68%)
	Pigmentation (cycles)		
	Cycles: 154/6560 (2.35%)	Cycles: 61/5716 (1.07%)	Not reported
	Headache (participants/cycles)		
	Cycles: 58/6560 (0.88%)	Cycles: 59/5716 (1.03%)	Participants: 124/350 (35.43%) Cycles: 1144/15 859 (7.21%)
	Epigastric pain (cycles)		
	29/6560 (0.44%)	120/5716 (2.10%)	Not reported
	Leucorrhoea (participants/cycles)		
	Cycles: 420/6560 (6.40%)	Cycles: 104/5716 (1.82%)	Participants: 209/415 (50.36%) Cycles: 404/11 472 (3.52%)

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence and additional considerations

Side effects

Quin 3 mg + LNG 6 mg	Quin 3 mg + NG 12 mg	Quin + Quin
Breast tenderness (participants/cycles)		
Cycles: 74/6560 (1.13%)	Cycles: 104/5716 (1.82%)	Participants: 112/1015 (11.03%) Cycles: 93/5804 (1.60%)
Hair loss (participants)		
Not reported	Not reported	1/759 (0.13%)

LNG: levonorgestrel; NG: norgestrel; Quin: quinestrol; Quin + Quin: quinestrol + quingestanol.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence and additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There was very low-certainty evidence from the one RCT and the case series for benefits and harms.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence and additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The GDG agreed that most women would probably place higher value on avoiding pregnancy.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence and additional considerations
● Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Given the harms that may be occurring with the Quin-NG and Quin-Quin, the GDG agreed that these would not be favoured. Because of the little evidence available for benefits and harms of Quin-LNG, the GDG agreed that it is probably not favoured.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence and additional considerations
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. Additional considerations QUIN formulations are low-cost to individuals.

Equity
What would be the impact on health equity?

Judgement	Research evidence and additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence found. The GDG agreed that a low-cost single monthly pill could improve equity, but it is unknown what is currently occurring. However, the GDG agreed that not providing these contraceptives in the method mix would not change equity.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	From the studies included in the systematic review:

Quin 3 mg + LNG 6 mg	Quin 3 mg + NG 12 mg	Quin + Quin
Discontinuation (participants)		
62/370 (16.76%)	111/362 (30.66%)	1073/2775 (38.67%)
Return to fertility		
Not reported	Not reported	2 studies: 290/290 (82% pregnant in < 12 months) and 118/256 (5% pregnant in 1–5 months) had return to menstruation

LNG: levonorgestrel; NG: norgestrel; Quin: quinestrol; Quin + Quin: quinestrol + quingestanol.

Additional considerations

The GDG agreed that many individuals would likely prefer to have a single monthly oral contraceptive pill. But if not available, individuals would find other contraceptives acceptable.

Feasibility Is the intervention feasible to implement?	
Judgement	**Research evidence and additional considerations**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Quin-LNG has been widely available with over 40 years of use. Quin-NG is not available to purchase (and does not seem to be available online). Pharmacovigilance is needed for adverse reporting and specific method used. Other contraceptive methods are available. It is probably feasible to add and to not add these contraceptives to the method mix.

Summary of judgements

	Judgement						
Desirable effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Undesirable effects	**Large**	Moderate	Small	Trivial		Varies	**Don't know**
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	**Favours the comparison**	**Probably favours the comparison**	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	●	○	○	○

Conclusions

Recommendation

WHO recommends against adding Quin-Quin to the contraceptive method mix for women of reproductive age (strong recommendation, very low certainty of evidence).

WHO recommends against adding Quin-NG to the contraceptive method mix for women of reproductive age (strong recommendation, very low certainty of evidence).

WHO suggests against adding Quin-LNG to the contraceptive method mix for women of reproductive age (conditional recommendation, low certainty of evidence).

***Remarks*: where quinestrol-containing products are being used, rigorous pharmacovigilance is needed to monitor safety. High-quality evidence about its efficacy and safety are needed.**

Justification

Overall, the GDG judged that there may be serious adverse events with Quin-NG and Quin-Quin and uncertain effects on benefits (e.g. no pregnancies). For Quin-LNG, the adverse effects are unknown and there are uncertain effects on benefits (e.g. pregnancies). The evidence overall for benefits and harms was very low, but the potential for harms with Quin-NG and Quin-Quin means a strong recommendation against those formulations. In addition, warnings about taking medicines not prescribed as dangerous, and pharmacovigilance with standard reporting of adverse events is needed. The GDG agreed that if these quinestrol formulations were not added to the contraceptive method mix, there are other contraceptives that can be used instead which would make not recommending them acceptable and feasible and likely have no impact on equity. The GDG however noted that more research into an oral contraceptive pill taken once monthly is needed.

Implementation considerations

The GDG did not discuss implementation considerations for recommendations relating to quinestrol-containing contraceptive pills.

A2.4 Recommendation: continuous or extended use of COCs

Should COCs be used: a) for extended durations up to six months or b) continuously up to one year versus cyclical use for contraception in women of reproductive age?	
Population	Women of reproductive age
Intervention	COCs used: a) for extended durations up to six months or b) continuously up to one year
Comparison	Cyclical use of COCs
Main outcomes	Number of pregnancies; Pearl Index; bleeding; amenorrhoea; side effects (e.g. headaches, nausea); serious adverse events (e.g. thrombosis) Acceptability, resources/costs, feasibility, equity
Setting	Outpatient
Perspective	Population
Background	The majority of COCs have a 28-day-cycle regimen: 21 active hormone pills followed by 7 days of placebo or no drug resulting in withdrawal bleeding every 28 days. Extended and continuous regimens have been explored and developed since the 1970s. While these regimens have been approved in some countries, these products are not always readily available, especially in low- and middle-income countries and resource-limited areas.
Conflicts of interest	None

Assessment

Desirable effects
How substantial are the desirable anticipated effects?

Judgement

- ○ Trivial
- ● Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

A systematic review was conducted up to October 2024 and found 18 RCTs and nine studies of other study design *(4)*.

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with cyclic	Risk difference with extended or continuous
Pregnancy	8337 (14 RCTs)	⨁⨁⨁◯ Moderate	OR 0.79 (0.41 to 1.52)	7 per 1000	**1 fewer per 1000 (from 4 fewer to 4 more)**
Pearl Index	2548 (3 RCTs)	⨁⨁⨁◯ Moderate	–	–	**0.2 lower (1.31 lower to 0.92 higher)**
Participants with no bleeding and no spotting (amenorrhoea)	1550 (6 RCTs)	⨁⨁⨁◯ Moderate	**All studies' findings favoured the continuous or extended-cycle use of COCs (i.e. more participants achieved amenorrhoea).**		
Total bleeding days (spotting + bleeding) during the 1-year study period	3474 (3 RCTs)	⨁⨁⨁◯ Moderate	–	–	**11.27 lower (21.15 lower to 1.4 lower)**

CI: confidence interval; GRADE: Grading, Recommendations, Assessment, Development and Evaluation; OR: odds ratio; RCTs: randomized controlled trials

Additional considerations

The GDG agreed that there is likely no difference between use of continuous or extended regimen compared to cyclic use for unexpected pregnancy or when measured with a Pearl Index. With extended or continuous regimens, more women will likely achieve amenorrhoea at 168 days and one year and have fewer bleeding days at one year. The studies also consistently showed that there will likely be fewer bleeding-only days but more spotting-only days with continuous or extended COCs. In addition, flexible regimens may result in less bleeding, but the evidence is uncertain.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

A systematic review was conducted up to October 2024 and found 18 RCTs and nine studies of other study design *(4)*.

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with no treatment	Risk difference with anticoagulant or other treatments
Participants with at least 1 adverse event	4634 (6 RCTs)	⨁⨁⨁◯ Moderate	OR 1.20 (1.03 to 1.41)	521 per 1000	45 more per 1000 (from 7 more to 80 more)
Severe adverse event	2090 (4 RCTs)	⨁⨁◯◯ Low	OR 0.69 (0.27 to 1.73)	33 per 1000	10 fewer per 1000 (from 24 fewer to 23 more)
DVT or VTE	RCTs and NRS	⨁⨁◯◯ Low	Four RCTs reported the number of DVT/VTE during the study period, resulting in an OR of 1.05 (95% CI: 0.16 to 6.79) (6/3104 in the continuous or extended COCs group vs 1/1373 in the cyclic COCs group, 0 fewer per 1000 [from 1 fewer to 4 more]). Three studies reported the occurrence of DVT/VTE related to the continuous/extended-cycle use of COCs, including one prospective cohort study of 727 flexible extended regimen users and two retrospective cohort studies of 236 284 continuous/extended-cycle COCs users. All three studies found a very low incidence of DVT/VTE in continuous/extended-cycle COCs users. In one study, there were two cases of DVT among 727 flexible extended regimen users during the second year of study. In another study, 35 and 68 patients developed VTEs among 25 593 treatment episodes in 91-day COCs-LNG and among 76 586 treatment episodes in 28-day COCs-LNG, respectively. In another study, there were 228 incident VTE cases identified in 210 691 noncyclic COCs users and 297 in 522 316 cyclic COCs users.		

CI: confidence interval; DVT: deep vein thrombosis; GRADE: Grading, Recommendations, Assessment, Development and Evaluation; LNG: levonorgestrel; NRS: non-randomized studies; OR: odds ratio; RCTs: randomized controlled trials; VTE: venous thromboembolism.

There was some discussion about the number of deep vein thrombosis (DVT) or VTE reported in the studies. Because some settings may not have adequate access to health care in case of a thrombosis, a small increase could be important. However, the GDG noted that the number of thrombotic events may not be higher than most contraceptives. The GDG agreed that there may be little to no difference in harms with extended or continuous COCs compared to cyclic regimens.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence and additional considerations
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Evidence of benefits was of moderate certainty and typically rated down for risk of bias due to high loss to follow-up. The evidence of adverse events was of low certainty, with risk of bias due to high loss to follow-up and few people in the studies, resulting in wide confidence intervals. Based on the low certainty of evidence of adverse events, the overall certainty is low.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence and additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The GDG agreed that most women would probably place higher value on avoiding pregnancy.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence and additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Given the small benefits (on which greater value is placed) and trivial harms but low certainty, the GDG agreed that extended or continuous cycle COCs are probably favoured over cyclic.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence and additional considerations
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. Additional considerations Instead, the GDG agreed that there is likely no additional cost when using extended or continuous COCs compared to cyclic since the same pack of medicine could be used. The GDG also noted that it may save on the costs of feminine products.

Equity
What would be the impact on health equity?

Judgement	Research evidence and additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence found. The GDG agreed that providing or taking continuous or extended COCs would probably not have a different impact on health equity than cyclic COCs.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Satisfaction was measured in 11 RCTs, two prospective cohort studies and one study using national survey data. In general, the continuous or extended-cycle use of COCs had a high level of satisfaction/acceptance. Nine RCTs (4176 participants) and all three studies of other study design (487 participants followed for four to five months) favoured the continuous or extended-cycle use of COCs in terms of satisfaction. Only two RCTs (582 participants) showed mixed results in satisfaction. Overall discontinuation was measured in 15 RCTs. There is moderate-certainty evidence that discontinuation may be slightly higher with continuous or extended COCs. However, the GDG agreed that counselling to explain to women the bleeding patterns would likely help reduce discontinuation, since the desire to bleed may be based on misinformation (where women think they need to bleed even when taking continuous/extended).

Feasibility
Is the intervention feasible to implement?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The GDG agreed that providing continuous or extended COCs would be feasible, but counselling and health-care involvement would be important to put in place.

Summary of judgements

	Judgement						
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

WHO suggests that COCs can be used for a) extended durations up to six months or b) continuously up to one year, as well as their cyclical use for contraception in women of reproductive age (conditional recommendation, low-certainty evidence).

***Remarks*: an extended regimen is defined as taking active combined hormonal contraceptive pills continuously for more than 28 days, followed by a planned hormone-free interval. Extended use may be for flexible or fixed duration. A continuous regimen is defined as taking active combined hormonal contraceptive pills every day without any breaks in daily pill-taking (no hormone-free interval).**

Justification

Overall, the GDG judged that there are likely small differences in the benefits of extended or continuous regimens compared to cyclic use, and the harms (e.g. VTE/DVT) are likely similar to other contraceptives and trivial. The GDG also agreed that effects may not vary by regimen or duration. Acceptability is also probably high, and there may be little difference in discontinuation between regimens. Extended or continuous regimens are probably feasible, resulting in negligible cost differences, and would not reduce equity. However, counselling for women should be provided to explain how to use these regimens and whether bleeding should occur or be expected.

Implementation considerations

When implementing this recommendation, the GDG underscored the paramount importance of the right to contraceptive choice. Further, the GDG emphasized the imperative of addressing the following overarching issues when applying continuous or extended COCs regimens to national programmes.

- Informed consent
- Elements of quality of care
- Essential screening procedures for administering COCs
- Provider training skills
- Referral and follow-up care for contraceptive use, as appropriate.

In addition, the GDG advised that WHO Member States should specifically consider the following when implementing continuous or extended COCs: offering continuous use of COCs should be done in the context of enhanced counselling (e.g. changes in bleeding patterns), which may not be practical in some settings; the ability to offer continuous or extended use regimens relies upon an adequate supply of commodities, which may not exist in all settings.

A2.5 Recommendation: extended use of etonogestrel contraceptive implants

Should etonogestrel (ETG) contraceptive subdermal implants be used up to five years versus three years in women of reproductive age?	
Population	Women of reproductive age
Intervention	ETG contraceptive subdermal implants up to five years
Comparison	ETG contraceptive subdermal implants up to three years
Main outcomes	Number of pregnancies; Pearl Index; bleeding; amenorrhoea; side effects (e.g. headaches, nausea); serious adverse events (e.g. thrombosis) Acceptability, resources/costs, feasibility, equity
Setting	Outpatient
Perspective	Population
Background	The ETG implant is a single rod of ethylene vinyl acetate copolymer containing 68 mg of ETG, covered in a rate-controlling membrane. The WHO *Selected practice recommendations for contraceptive use guideline* (SPR) describes product labelling regarding length of use for: "Implanon NXT (also known as Nexplanon; replaces Implanon) which is a 1 rod containing etonogestrel, labelled for up to 3 years of use". Although labelled for use up to three years, the consistent serum levels observed at the end of the three-year period of use suggest that the implant could continue to provide effective contraception beyond the approved duration.
Conflicts of interest	None

Assessment

Desirable effects
How substantial are the desirable anticipated effects?

Judgement

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

A systematic review of studies up to 8 November 2024 found six studies comparing the extended interval use of ETG implant for contraception beyond three years to the currently approved duration of three years *(5)*.

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects (95% CI)	
			Risk within 3 years	Risk after 3 years
Contraceptive efficacy within 3–5 years compared with contraceptive efficacy within 3 years (assessed with: Pearl Index)	– (2 single-arm cohort studies)	⨁⨁◯◯ Low	**Pearl Index was 0/100 woman-years in Ali *(6)* and McNicholas *(7)*. Pearl indices in Moray *(8)* systematic review of ETG implant efficacy ranged from 0 to 1.4/100 woman-years in 5 studies**	
Contraceptive efficacy within 3–5 years compared with contraceptive efficacy within 3 years (assessed with: pregnancy rate)	1249 (2 single-arm cohort studies)	⨁⨁◯◯ Low	**3/943 (0.3%)**	**0/306 (0.0%)**
Contraceptive efficacy within 3–4 years compared with contraceptive efficacy within 3 years (assessed with: Pearl Index)	– (6 single-arm cohort studies)	⨁⨁◯◯ Low	**Pearl Index was 0/100 woman-years in Ali *(6)* and McNicholas *(7)*. Pearl indices in the Moray *(8)* systematic review of ETG implant efficacy ranged from 0 to 1.4/100 woman-years in 5 studies**	
Contraceptive efficacy within 3–4 years compared with contraceptive efficacy within 3 years (assessed with: pregnancy rate)	2843 (6 single-arm cohort studies)	⨁⨁◯◯ Low	**3/1983 (0.2%)**	**0/860 (0.0%)**

CI: confidence interval; ETG: etonogestrel; GRADE: Grading, Recommendations, Assessment, Development and Evaluation.

Additional considerations

The GDG agreed that there may be no difference in pregnancies with implant use up to three years or five years.

The GDG discussed whether there could be differences in efficacy based on BMI. However, some laboratory evidence suggests that there may be no differences (e.g. serum levels are not lower if BMI is greater). Therefore, the GDG agreed that efficacy may be similar regardless of BMI.

Undesirable effects
How substantial are the undesirable anticipated effects?

Judgement

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

Research evidence and additional considerations

A systematic review of studies up to 8 November 2024 found six studies comparing the extended interval use of ETG implant for contraception beyond three years to the currently approved duration of three years *(5)*.

Outcomes	Number of participants (studies) follow-up	Certainty of the evidence (GRADE)	Anticipated absolute effects (95% CI)	
			Risk within 3 years	Risk after 3 years
Greater than one attempt at removal	1020 (2 single-arm cohort studies)	⨁◯◯◯ Very low	0/818 (0.0%)	0/202 (0.0%)
Nonpalpable implant requiring referral	1070 (3 single-arm cohort studies)	⨁◯◯◯ Very low	0/843(0.0%)	1/227 (0.4%)
Implant breakage	1020 (2 single-arm cohort studies)	⨁◯◯◯ Very low	0/818 (0.0%)	0/202 (0.0%)
Infection at 4 and 5 years	1020 (2 single-arm cohort studies)	⨁◯◯◯ Very low	0/818 (0.0%)	0/202 (0.0%)
Neurological sequelae of removal/ attempted removal at years 4 and 5	1020 (2 single-arm cohort studies)	⨁◯◯◯ Very low	0/818 (0.0%)	0/202 (0.0%)
Other adverse events related to the implant	1020 (2 single-arm cohort studies)	⨁◯◯◯ Very low	0/818 (0.0%)	0/202 (0.0%)

CI: confidence interval; GRADE: Grading, Recommendations, Assessment, Development and Evaluation.

Additional considerations

The GDG agreed that although the evidence is uncertain about the safety of extended use, the studies did not report any events for up to three- or five-year intervals (except for one woman out of 227 who had the implant up to five years and required a referral for removal).

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence and additional considerations
● Very low ○ Low ○ Moderate ○ High ○ No included studies	Evidence for benefits was of low certainty and typically rated down for risk of bias because there were no direct comparisons of length of time within a study; and there were few people across the studies. The evidence for adverse events was of very low certainty for similar reasons. Based on the very low-certainty evidence of adverse events, the overall certainty is very low.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence and additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The GDG agreed that most women would probably place higher value on avoiding pregnancy.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence and additional considerations
○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Given that there may be trivial differences in benefits and harms between using the implant up to three or five years, the balance does not favour one over the other.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence and additional considerations
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was found. Additional considerations Instead, the GDG agreed that since fewer visits and procedures would be needed if use of the implant was extended up to five years, the costs to the patient and health-care system could be slightly reduced. However, it would not have a moderate or large impact on costs.

Equity
What would be the impact on health equity?

Judgement	Research evidence and additional considerations
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence found. The GDG agreed that extending its use would probably not have an impact on equity.

Acceptability
Is the intervention acceptable to key stakeholders?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One study (204 participants) assessed acceptability of the implant within three to five years measured by bothersome bleeding prompting removal. The proportion of bothersome bleeding prompting removal during this timeframe was 11/204. Four studies (494 participants) assessed acceptability of the implant within three to four years measured by bothersome bleeding prompting removal. The proportion of bothersome bleeding prompting removal during this timeframe was 15/494. Additional considerations The GDG agreed that the proportions were trivial, and extending its use is probably acceptable. The GDG also indicated that there could be some confusion that women who do not remove it may think they can become pregnant after the three years. The GDG expressed some concern that clinicians may not offer replacement at three years if extended use was available, but information would need to be provided to ensure women could receive what they prefer.

Feasibility
Is the intervention feasible to implement?

Judgement	Research evidence and additional considerations
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don’t know	The GDG agreed that using the implant for up to five years would not require any infrastructure changes where it is currently available. Additional education for women may be necessary given concerns with understanding of extended use (see acceptability section). Ongoing education is needed for clinicians on how to remove implants (regardless of how long the client has had it, whether up to three or five years).

Summary of judgements

	Judgement						
Desirable effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	**Trivial**		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	**Does not favour either the intervention or the comparison**	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

WHO suggests ETG contraceptive implants can be used for up to five years, in line with the updated manufacturer's approved duration of five years (conditional recommendation, very low-certainty evidence).

Justification

There is very low-certainty evidence that extended use of ETG contraceptive implants up to five years may be as effective and safe as implants up to three years. The longer duration is probably acceptable to women and clinicians and would have little impact on equity, but could reduce resources associated with visits, procedures and costs. Implants up to five years are probably as feasible to provide as up to three years and would not require additional implementation strategies.

Implementation considerations

When implementing this recommendation, the GDG underscored the paramount importance of the right to contraceptive choice. The GDG emphasized the imperative of addressing the following overarching issues when applying extended use of ETG implants to national programmes.

- Informed consent
- Elements of quality of care
- Essential screening procedures for administering ETG implants
- Provider training skills
- Referral and follow-up care for contraceptive use, as appropriate

The GDG advised that WHO Member States should specifically consider the following when implementing extended use of ETG implants.

- A client's right to contraceptive choice and how long they wish to use an implant must be assured.
- Irrespective of the option to extend implant use, programmes and providers must safeguard a client's right to have their implant removed when they wish.
- Additional training and communication materials may be needed for providers to implement extended implant use.

Lastly, the GDG encourages WHO Member States to continue to enable access to implant removals, as well as opportunities to train clinicians to remove implants.

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For more information, please contact:

UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Department of Sexual, Reproductive, Maternal, Child, Adolescent and Ageing Health (LHR).

World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

Email: srhcfc@who.int
Website: https://www.who.int/hrp;
https://www.who.int/health-topics/contraception
www.who.int