

Norms, standards and processes underpinning development of WHO recommendations on vector control

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Note. The original title *Norms, standards and processes underpinning WHO vector control policy development* was changed to reflect recent changes to WHO's use of language regarding "policy" and "recommendations". The text has been updated accordingly.

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INTRODUCTION

In 2018, the World Health Organization (WHO) reviewed its processes for developing and disseminating guidance and recommendations spearheaded by a detailed analysis conducted within the Global Malaria Programme (GMP). The review identified areas for improvement, one of which is the better communication of the norms, standards and processes underpinning these recommendations. Better communication will ensure that product developers and researchers are fully aware of the WHO's requirements for assessing and ultimately recommending interventions for vector control. In this context, a vector control intervention is defined as a tool, technology or approach/strategy, and thus is not limited to products (see Annex 1 for glossaries of terms).

The current evaluation process for vector control was first communicated in 2017, following the transition from the WHO Pesticide Evaluation Scheme (WHOPES) to a process co-managed by the WHO Prequalification Team for Vector Control Products (PQT-VCP) and the two technical departments involved in vector control: GMP and the Department of Control of Neglected Tropical Diseases (NTD). While PQT-VCP assesses the safety, quality and efficacy of all vector control products and interventions, the three departments together support the Vector Control Advisory Group (VCAG), which is tasked with evaluating the public health value of novel interventions for which no WHO recommendation exists.

Since this first communication, the evaluation process and associated communication have been refined and continue to evolve. The implementation of the new process for developing WHO recommendations provides an opportunity to communicate these developments within the overarching framework of the WHO revised process, while highlighting the elements specific to vector control.

This document is mainly aimed at manufacturers and procurers of vector control products, and at researchers generating data, technologies and approaches/strategies. However, it is also envisaged that this document will provide reassurance to WHO Member States regarding the rigour applied by WHO in formulating recommendations, considering that such recommendations are used by Member States to inform the development of national policy and implementation of strategies.

The document provides a detailed overview of the norms, standards and processes underpinning the development of WHO recommendations for vector control interventions.¹ It also includes high-level information on the prequalification process, which is complementary to and coordinated with development of WHO recommendations. Detailed information on prequalification requirements and processes are available on the PQT-VCP website (<https://www.who.int/pq-vector-control/en/>).

In addition, this document provides an overview of the roles and responsibilities of the two technical departments involved in the development of vector control recommendations, namely GMP and NTD, and how they interact with PQT-VCP, which oversees the prequalification process in this area (see Annex 2). A RACI matrix is used to describe the various roles in completing the required tasks or deliverables for the vector control evaluation process the associated norms, standards and process of developing WHO recommendations. RACI is an acronym derived from the four key responsibilities most typically used: Responsible, Accountable, Consulted and Informed.

¹ This document replaces: The evaluation process for vector control products. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/255644>) and Malaria vector control policy recommendations and their applicability to product evaluation. Geneva: World Health Organization; 2017.



THE PROCESS OF DEVELOPING WHO RECOMMENDATIONS

A revised process for developing WHO recommendations is being rolled out across WHO departments beyond GMP, structured around three high-level steps:

- **Better anticipate:** This step involves activities that build up to and trigger the process for developing WHO recommendations, including horizon scanning and developing or endorsing preferred product characteristics (PPCs)/target product profiles (TPPs), in order to stimulate innovation, guide product development and provide predictability to manufacturers with respect to the evaluation process anticipated for these new tools.
- **Develop recommendations:** In this step, activities are undertaken to develop WHO recommendations, including recommendations based on the generation of evidence by manufacturers and/or research groups to demonstrate that an intervention has public health value; the assessment of these data by the relevant WHO advisory groups; and the formulation of recommendations by WHO.
- **Optimize uptake:** WHO guidance and recommendations are disseminated and use monitored.²

As outlined in Fig. 1, these process enhancements enable WHO to identify and communicate unmet public health needs; develop recommendations through an open and transparent process with shortened timelines; and optimize uptake through the use of tools such as digital technology.

This document outlines the links between the evolution of the process for developing WHO recommendations and the evolution of the evaluation process for vector control interventions. It also describes how the outputs from this evaluation process inform the development of new WHO recommendations. Topics covered include the determination of the evaluation pathways (Prequalification Pathway or New Intervention Pathway), detailed steps to be followed by applicants, and key epidemiological evaluation standards for vector control interventions, including study design and WHO requirements for trials.

OVERVIEW OF THE EVALUATION PROCESS FOR VECTOR CONTROL INTERVENTIONS

The WHO process for evaluating vector control interventions consists of two separate yet complementary pathways (Fig. 2). To decide which pathway an intervention will follow, the WHO Pre-submission Coordination Committee (PCC)³ determines whether or not a new submission falls into an existing intervention class, based on the categorization of interventions in the table “Overview of interventions under VCAG review” on the VCAG website (and see “Identification of class and determination of pathway” below).⁴ In vector control, an intervention class is a group of interventions that share a common entomological effect, mechanism and use pattern through which they reduce pathogen transmission, and thus reduce infection and/or disease in humans.

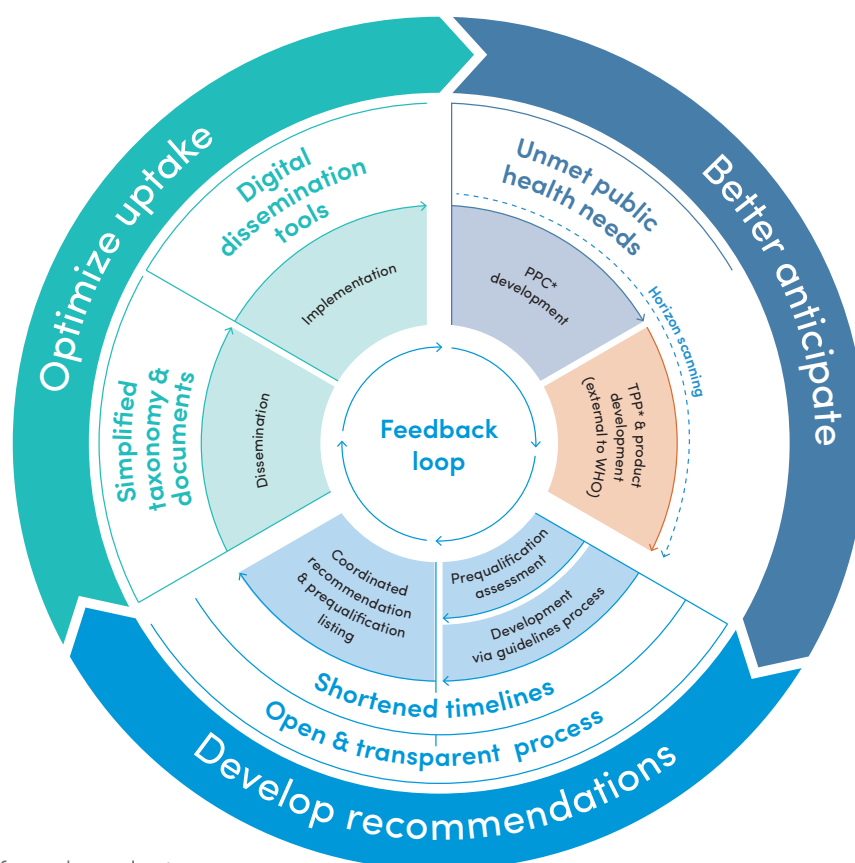
Interventions that fall into a class already covered by a WHO recommendation will be assigned to the Prequalification Pathway to assess the intervention’s safety, quality and entomological efficacy (see “Prequalification Pathway” below). No epidemiological trials are required, given that the intervention’s impact on infection and/or disease – also termed public health value – has already been demonstrated by the first-in-class intervention that received a WHO

² For more information on the policy-making process, please see <https://www.who.int/teams/global-malaria-programme/guideline-development-process>.

³ The Pre-submission Coordination Committee (PCC) is made up of staff members from the three WHO units responsible for managing VCAG: GMP, NTD and PQT-VCP.

⁴ The table can be accessed at: <https://www.who.int/groups/vector-control-advisory-group>.

Fig. 1. High-level diagram of GMP's recommendation pathway for new products.² The work of VCAG falls under the orange sector of "Better anticipate": "TPP & product development".



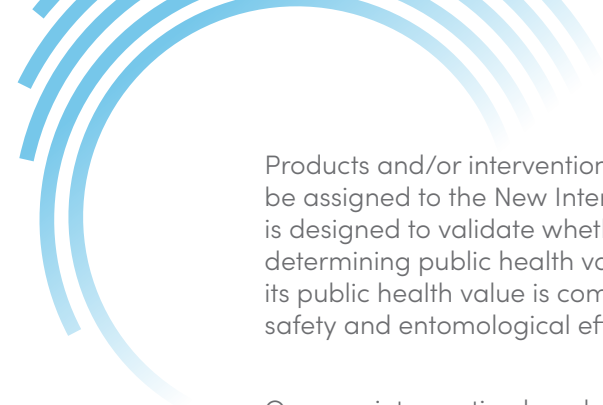
*PPC: Preferred product characteristic

*TPP: Target product profile

recommendation. Once the safety, quality and entomological efficacy of the intervention have been demonstrated, it will be prequalified and added to the listing of prequalified products by PQT-VCP.² If the formulation of the product changes, PQT-VCP will need to be consulted to make sure the product maintains the same specifications.

The prequalification process includes a review of data supporting the quality, safety and efficacy of the intervention. The data are compiled into a dossier that conforms to a standard format. The process also involves inspection of the manufacturing/production site(s). This information, in conjunction with other procurement criteria, is used by the United Nations (UN) and other procurement agencies to make purchasing decisions. Due to the stringent assessment of the prequalification process, many governments also base their procurement on the prequalification listing of vector control interventions instead of conducting an independent evaluation. Unfortunately, WHO cannot utilize or deploy philanthropic donations of interventions if they are not yet prequalified and/or validated as having public health value.

Issuing a PQT-VCP listing is dependent on there being a WHO recommendation for a product class that covers the specific intervention to be prequalified. WHO recommendations in the area of vector control are developed by GMP and/or NTD, depending on the use pattern of the intervention. Such WHO recommendations are communicated via guidelines documents, for example, the *Guidelines for malaria vector control (1)*. The publication of a WHO recommendation jointly with a PQT-VCP listing provides a single WHO position on the Organization's recommendations for vector control, including specific tools and technologies. This information is intended to support WHO Member States in the design and implementation of their vector control and disease elimination strategies.



Products and/or interventions belonging to a class not covered by a WHO recommendation will be assigned to the New Intervention Pathway, described in further detail below. This pathway is designed to validate whether the intervention has public health value. WHO's process for determining public health value is supported by VCAG. VCAG's review of any new intervention for its public health value is complemented by a PQT-VCP assessment of the intervention's quality, safety and entomological efficacy.

Once an intervention has demonstrated public health value, it is termed a first-in-class product, and WHO will convene a Guideline Development Group (GDG) to formulate a WHO recommendation. As outlined by the WHO Guidelines Review Committee (GRC) in Annex 3, the body of evidence that informs the recommendations in WHO guidelines includes:

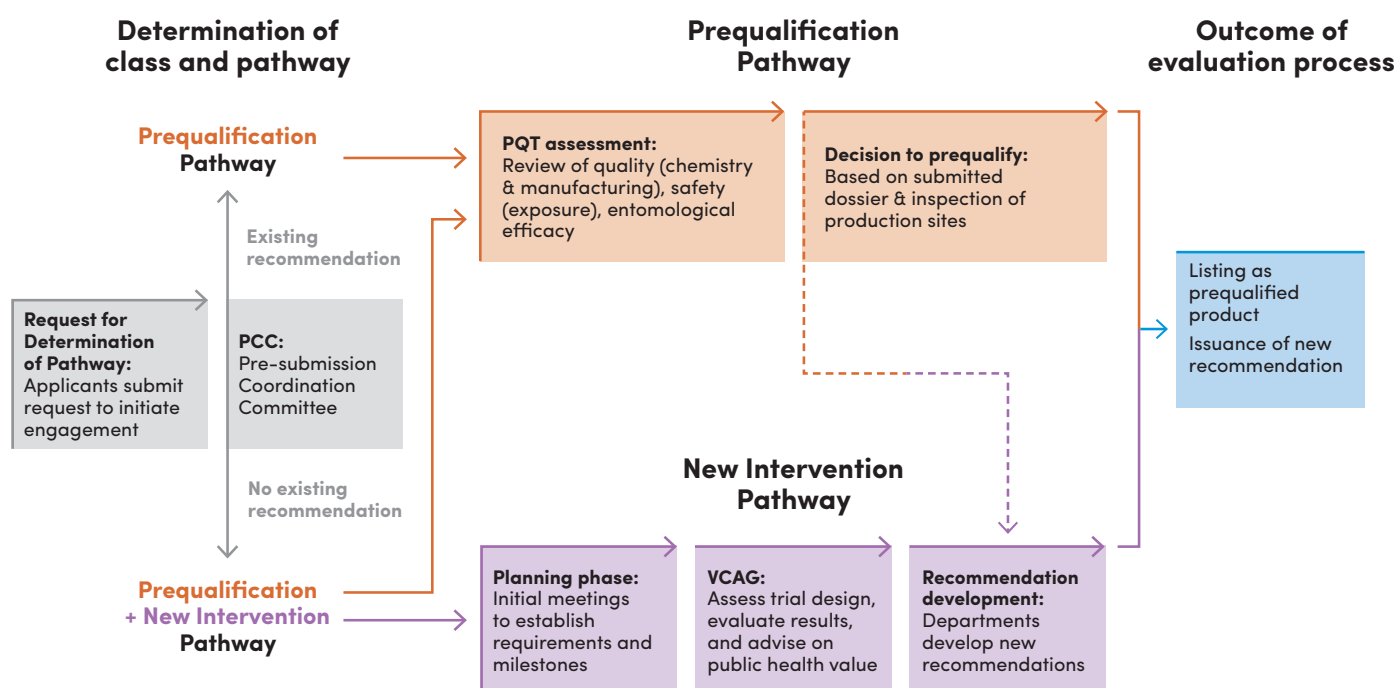
- all types of study designs that are appropriate to the question(s) underlying a recommendation, and according to other relevant considerations;
- primary data, research studies or systematic reviews;
- evidence from multiple sources;
- publicly available evidence.

Further to this, VCAG's recommendations and PQT-VCP's evaluation of the intervention's safety, quality and efficacy are also provided to the GDG to inform its deliberations on a specific WHO recommendation. The GDG's outputs will be an evidence-to-decision table and GRADE assessment. These will be presented to the relevant policy advisory group(s) – the Strategic and Technical Advisory Group (STAG) for NTD and Malaria Policy Advisory Group⁵ (MPAG) for GMP – for review and endorsement, before being formally submitted to the GRC in the form of a revised guideline document that includes the new WHO recommendation. Once GRC approval is granted, the new recommendation and its supporting information will be made available online. From early 2021, all WHO recommendations on malaria will be accessible via MAGICapp (<https://app.magicapp.org/#/guideline/6287>).

Following validation of an intervention's safety, quality and entomological efficacy, it will be prequalified and listed. To the extent feasible, the two processes will work in parallel to ensure that a prequalification listing can be published alongside a new WHO recommendation. The exact timing is dependent on the speed with which epidemiological studies are planned and implemented, as well as on PQT-VCP promptly receiving a dossier with a full data package (explained in more detail in the following section) to support its review. It is envisioned that the WHO evaluation process will evolve to a stage where the two pathways are fully synchronized so that WHO recommendations and prequalification decisions can be communicated simultaneously. In this context, it should be noted that a WHO recommendation is a prerequisite for a prequalification listing and can no longer be preceded by such listing.

⁵ Formerly called the Malaria Policy Advisory Committee (MPAC).

Fig. 2. Evaluation pathway for vector control interventions



Determination of class and pathway

Request for Determination of Pathway

The evaluation of vector control interventions commences when a product developer, manufacturer or researcher, referred to henceforth as the “applicant”, submits a “Request for Determination of Pathway (RDP)” via the single entry portal managed by PQT-VCP (pqvectorcontrol@who.int). The RDP is then processed for consideration by the PCC for vector control interventions.⁶

Pre-submission Coordination Committee

The PCC consists of staff from PQT-VCP, GMP and NTD. The PCC will consider the submitted RDP and compare the intervention description, including its entomological effect, mechanism of action, and anticipated use pattern (e.g., whether an insecticide is intended for use as a larvicide or for indoor residual spraying) against WHO’s categorization of vector control intervention types and classes.⁴ The PCC will assess whether the intervention belongs to a class already covered by a WHO recommendation, and hence is assigned to the Prequalification Pathway, or whether complementary assessment in the New Intervention Pathway is required to determine public health value. If interventions have more than one anticipated use pattern, each use pattern will require separate assessments of the appropriate modules (see “Prequalification assessment” below) and VCAG evaluation.

The PCC will provide feedback to the applicant through PQT-VCP, describing the applicable pathway(s) and the rationale for the determination. A WHO focal point(s) will be assigned to the intervention to support the applicant through the process.

⁶ The task of the PCC is to determine whether or not the proposed intervention is supported by an existing WHO recommendation; and to provide a coordination mechanism between the departments on WHO recommendation updates, implementation, prequalification assessments of products, and prequalification listings concerning vector control interventions.



Prequalification Pathway

Irrespective of whether an intervention is first-in-class or whether a WHO recommendation supporting its use is already in place, all new products must undergo the prequalification evaluation if they are to be listed as a prequalified intervention. PQT-VCP ensures that vector control products are effective, safe, and meet stringent quality and manufacturing standards. The team assesses product dossiers, inspects manufacturing sites and supports quality-control testing of products as appropriate. The Prequalification Pathway for vector control products is managed by PQT-VCP, under the Regulation and Prequalification Department of the Medicines and Health Products Division.

Prequalification assessment

For all new interventions (including both products and technologies), the applicant is required to submit an application for prequalification to PQT-VCP. This includes the submission of a dossier compiled according to the PQT-VCP standard format. The dossier includes a full data package to support the assessment of the intervention's quality, safety and entomological efficacy, along with its proposed label information and/or product information. Six modules are included in the submission dossier: Module 1: Administrative Information and Labelling; Module 2: Discipline Summaries; Module 3: Quality (chemistry and manufacturing); Module 4: Safety (hazard, exposure, and risk); Module 5: Efficacy (efficacy to target vectors); and Module 6: Inspections (Site Master Files). More information about each module can be found at: <https://extranet.who.int/pqweb/>.

Once submitted, the application will be screened to ensure that all the required information and data are included in the dossier. When the PQT-VCP evaluation is completed and found to support a prequalification decision, PQT-VCP will review the label information and provide advice to the manufacturer based on the assessment. Part of the prequalification assessment also involves inspections of the manufacturing/production site.

Decision to prequalify

PQT-VCP's decision on whether to prequalify a product will be made based on the data and information to support the use of the product and inspection of the manufacturing facilities. Once the product is prequalified, the applicant will be informed and the product will be listed on the WHO PQT-VCP website (<https://extranet.who.int/pqweb/vector-control-products>). The listing will be linked to current, updated or new WHO recommendation(s).

PQT-VCP is responsible for monitoring the intervention throughout its life cycle. This includes any changes made to the product (formulation, use, claims, etc.), monitoring and surveillance, complaints and product testing in collaboration with partners, and periodic monitoring of manufacturing sites.

New Intervention Pathway

Interventions without a WHO recommendation will follow the New Intervention Pathway, which complements the Prequalification Pathway. The New Intervention Pathway is designed to help substantiate an intervention's public health value and, in doing so, to support the development of an evidence base to inform deliberations on a WHO recommendation by a GDG. This evaluation pathway is jointly managed by all three departments (GMP, NTD and PQT-VCP) and is supported by VCAG. VCAG is a WHO advisory group that assesses the public health value of new vector control interventions submitted to WHO.⁷ As described in the VCAG Standard Operating Procedures, the advisory group consists of up to 15 members (who may be joined by temporary advisors on an ad hoc basis) (2). These experts provide guidance to applicants on the generation

⁷ WHO VCAG website: <https://www.who.int/groups/vector-control-advisory-group>

of epidemiological data and study designs, and assess the public health value of new vector control interventions (3).

As VCAG guides the generation of epidemiological evidence to support the assessment of public health value, it is expected that preliminary entomological data from field and/or semi-field studies will have been collected prior to any VCAG submission.⁸

Planning phase

After assignment to the New Intervention Pathway, an initial meeting is held with the applicant, GMP/NTD and PQT-VCP to outline WHO requirements and define the way forward.

To initiate interaction with VCAG, the applicant must complete the VCAG Application Form.⁹ An initial meeting between the applicant and the WHO VCAG Secretariat will be held to discuss plans for epidemiological studies and other associated research.

As guiding principles, it would generally be expected that, prior to interacting with VCAG, applicants consider in their planning factors that may potentially influence their study outcomes. Such considerations may include (but are not limited to):

- spatial, temporal and historical heterogeneity in disease prevalence in the study location;
- spatial and temporal heterogeneity in vector prevalence;
- ecological diversity, with specific attention to variation in vector ecology within and between the selected study sites;
- variation in vector behaviour (that may be influenced by the intervention itself throughout the duration of the study).

As the strength of a WHO recommendation is influenced by the weight and strength of the available evidence, applicants are encouraged to consider testing their intervention across different geographic settings. The term 'geography' in this sense is not restricted to physical geography, but encapsulates other epidemiologically relevant factors, including local ecologies of co-circulating (and potentially interacting) pathogens, differences in vector ecology, and climatic factors.

Interaction with VCAG

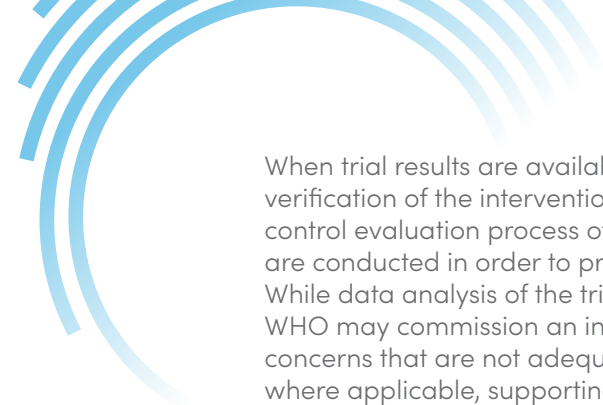
All communication between VCAG and the applicant will be through the WHO VCAG Secretariat. Through WHO, VCAG will support applicants with the development of epidemiological study design, and related data generation and assessment, including review of draft protocols and associated documents.¹⁰ VCAG will review and assess trial results submitted by applicants for new vector control interventions and may additionally draw on entomological data to support the assessment of the epidemiological results.

Formal written feedback on study protocols and data from trials will be through VCAG meeting reports. If changes related to the evaluation of a specific intervention are made, such as to the protocol or statistical analysis plan, these changes should be communicated to the WHO VCAG Secretariat.

⁸ It is, however, acknowledged that for some novel interventions that raise ethical concerns (e.g., genetically modified organisms), semi-field and field studies may not be possible in all situations and only data derived from laboratory studies will be available.

⁹ The application form will be emailed to applicants directly by the VCAG Project Manager.

¹⁰ Associated documents include but are not limited to statistical analysis plans, SOPs and study designs.



When trial results are available, they should be submitted to WHO for VCAG's assessment and verification of the intervention's public health value against the targeted disease(s). The vector control evaluation process of WHO requires that at least two trials with epidemiological endpoints are conducted in order to provide some reassurance that the study results are reproducible.¹¹ While data analysis of the trial results is to be conducted by the investigator(s) of the studies, WHO may commission an independent analysis of raw data if VCAG identifies potential concerns that are not adequately addressed by applicants. Once epidemiological data and, where applicable, supporting entomological data for a new intervention have been reviewed, VCAG will provide WHO with an assessment of the data, including the extent to which the data demonstrate public health value. This assessment provides the foundation for the development of the new WHO recommendation by a WHO GDG. Once new guidelines have been developed, other interventions subsequently submitted to WHO that share the characteristics of the given intervention class will not be required to conduct epidemiological trials.^{4,12}

Development of WHO recommendations

Once VCAG provides WHO with its assessment of an intervention's public health value, a GDG will be convened by the relevant department. The GDG will review the assessment, as well as other evidence that may have been generated outside of the WHO evaluation process, and deliberate on a WHO recommendation.

The available evidence will be assessed using the GRADE methodology, which provides a tool to systematically judge the quality of a body of evidence and the strength of recommendations derived from that evidence. Detailed criteria that will be considered when moving from evidence to decision, include (but are not limited to) the quality of the evidence, the balance of benefits and harms, resource implications, the priority of the problem, equity and human rights, acceptability and feasibility (4). An evidence-to-decision table outlines how these factors informed the process of developing a specific WHO recommendation and determined its direction and strength. Such tables enhance the transparency of the process, focus the discussions of the GDG, and permit recording of the judgements made about each factor and how each one contributed to the recommendation.

The GDG's recommendations on an intervention, including its appropriate application and scope, will be presented to the relevant advisory group of each department.¹³ Any suggested modification will be returned for reconsideration by the GDG. A revised recommendation will be accepted by the relevant advisory group and Director, on behalf of the Director-General.

Finally, the WHO GRC will then review, provide feedback and subsequently approve the updated guidelines that include the new WHO recommendation, and the accompanying evidence-to-decision table.

Outcomes of the evaluation process

While a WHO recommendation supporting the public health value of a new intervention is being developed, assessment of the data supporting a product's safety (for its intended use pattern), quality and entomological efficacy occurs in parallel. Once the WHO recommendation is published in a revised guideline, the new intervention will be added to the list of prequalified interventions.

¹¹ Two epidemiological trials is the minimum requirement for WHO to initiate the process of evidence review and formulation of WHO recommendations.

¹² Evaluation of an intervention's safety, quality and efficacy will still be required, as assessed through the Prequalification Pathway.

¹³ STAG for NTD and MPAG for GMP

EPIDEMIOLOGICAL EVALUATION STANDARDS FOR VECTOR CONTROL INTERVENTIONS

WHO's process for developing recommendations for new vector control interventions relies on evidence from well-designed and well-conducted trials with epidemiological endpoints to demonstrate the public health value of the intervention.

Applicants are strongly advised to work closely with statisticians and epidemiologists to conduct epidemiological trials, and engage with VCAG early in the protocol development process in order to ensure that trial data meet WHO's standards for determining public health value. WHO requires studies to be conducted in compliance with international ethical standards and good clinical and laboratory practices. Guidance in this area is readily available (5). For information on reporting randomized controlled trials (RCTs), the Consolidated Standards of Reporting Trials (CONSORT) website outlines the minimum set of recommendations for reporting randomized trials (<http://www.consort-statement.org/>). It also offers a standardized approach for presenting trial findings, which facilitates complete and transparent reports, and critical appraisal and interpretation.

The WHO norms and standards that guide VCAG's advice on the generation of epidemiological data and study designs for trials assessing the public health value of novel vector control interventions are outlined below.

Number of trials

Within WHO's vector control evaluation process, a minimum of two trials with epidemiological endpoints is required to initiate convening the GDG. This minimum number is based on the need to demonstrate that any observed public health value is replicable across settings.

If the initial two studies generate contradictory or inconsistent results or suffer from design limitations that preclude comprehensive assessment of an intervention's potential public health value, further trials with epidemiological endpoints may be required.


Types of trials

At present, RCTs are considered the gold standard of vector control trial design for generating data to inform WHO recommendations. However, the WHO guidelines development process will consider evidence generated from other trial designs also (Annex 3).

Work is ongoing to both investigate the rigour of trial designs other than RCTs and assess whether entomological endpoints can be identified that reliably correlate with epidemiological endpoints and can act as surrogates. Once results of these ongoing efforts are available, WHO will review these with a view to potentially modifying its guidance on the trial endpoints required for assessment of public health value.

Choice of trial sites

Given that interventions are generally deployed across different epidemiological settings, WHO recommends conducting the two trials in geographically separate settings, enabling independent replication of study outcomes.



Applicants are expected to consider the choice of study setting and its appropriateness for meeting trial objectives, and should be able to justify this decision in their interaction with VCAG. Several guiding principles are offered under “Planning phase”.

Trial duration

Applicants should design their trials with durations that consider the characteristics of the intervention and its intended deployment, expected durability/residual efficacy and replacement intervals, and the epidemiology (e.g., pathogen transmission intensity) of the selected study site.

It should be noted that for insecticide-treated nets (ITNs), the minimum intervention period of the study should be two years, excluding the period of baseline data collection; a third intervention year is strongly encouraged to demonstrate continued impact over the anticipated life of the net. The VCAG assessment may be initiated once data from two 24-month intervention trials are available in order to determine whether these confirm public health value. Data from a third year of intervention, once available, will facilitate refinement of the associated evidence-to-decision table.

Although in the past VCAG has requested trial durations of either two transmission seasons or two calendar years, WHO does not stipulate trial durations of two years for any intervention other than ITNs. For other interventions, the trial duration may be shorter (or longer) depending on the characteristics of the intervention, the study design and the study setting. Applicants are free to propose the duration they consider appropriate, and VCAG will request justifications for the proposed trial durations. Applicants are encouraged to focus on trial durations that maximize the likelihood that the study objectives and targeted statistical power will be robustly achieved so as to strengthen the evidence used to inform deliberations on a WHO recommendation.

In addition, where appropriate, applicants are advised to consider factors that might influence the long-term efficacy of an intervention (including behavioural or genetic adaptation to the existence of the intervention). If there are immediate concerns over the rapid loss of efficacy of a product, it is recommended that the trial duration be adjusted to generate data to assess this concern.

Primary epidemiological endpoints

To determine the epidemiological impact of a vector control intervention, the preferred endpoints are generally the incidence of disease and/or detection of new infections in humans. In situations where infection is chronic, or an infection frequently manifests sub-clinically, the prevalence of pathogen infection (or prior infection) is warranted. Prevalence may also be used as a secondary trial endpoint for those trials designed to collect incidence data.

Epidemiological outcomes

VCAG will consider whether an intervention has demonstrated a statistically significant epidemiological impact over the control arm (which should include the standard of care in the study setting).

Applicants will be expected to prepare and submit their statistical analysis plans in advance of the trial, with a clear indication of the a priori hypothesis, target effect sizes and levels of significance, justified by appropriate power calculations. As with any clinical trial, any and all deviations from the approved statistical plan and post-hoc analyses should be accompanied by adequate justification.

Neither WHO nor VCAG stipulates a specific target effect size for the primary endpoints of trial outcomes. Applicants are encouraged to consider a contextually relevant effect size that is likely to be appropriate for the intended deployment environment. The strength of WHO recommendations developed for a given intervention will be guided by the magnitude of the observed effect in associated trials.



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5. Good clinical laboratory practice (GCLP). Geneva: World Health Organization; 2009 (<https://apps.who.int/iris/handle/10665/44092>).

ANNEX 1. GLOSSARIES

Key terms

biochemical mode of action	A biochemical mode of action describes the manner in which pesticides interfere with the biochemistry of animals and plants.
biological agent	In the context of vector control interventions, this refers to the exploitation of an organism's parasitic behaviour, predation or other biological mechanisms (such as sterilization) to control target vectors, and/or their ability to transmit a pathogen. Examples may include bacteria, fungi or insect-specific viruses that infect vectors, or indeed the sterilized vectors themselves.
entomological effect	Entomological effect refers to a product's effect on a disease vector in terms of killing, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects; for example, indoor residual spraying (IRS) formulations with pyrethroids and carbamates differ in their biochemical modes of action, yet are considered to have a similar impact on the target insect in areas of insecticide susceptibility.
first-in-class	First-in-class refers to the first intervention with a novel entomological effect. The intervention classification table is used in the process of determining classes. The public health value of a first-in-class product is ascertained by VCAG based on the demonstration of epidemiological efficacy against human infections and/or disease. Once the public health value of a first-in-class product has been ascertained, a new product class is established.
GRADE	The "Grading of Recommendations Assessment, Development and Evaluation" method is a systematic and explicit approach to making judgements about the quality of a body of evidence and the strength of recommendations made from that evidence.
intervention	The term intervention in this context applies to any new vector control product/tool, technology or strategy/approach to control a vector population.
intervention class	<p>The intervention class is defined as a group of interventions with a similar entomological effect and mechanism by which the effect is derived. For interventions that fall within the same intervention class, two trials with epidemiological endpoints must demonstrate a significant reduction in the primary epidemiological endpoint for that intervention to be confirmed as an established class, with a WHO recommendation and associated prequalification listing.</p> <p>Note that for many interventions, different target diseases will mean that the interventions fall into different classes, because the epidemiological effect needs to be substantiated against each group of vector-borne diseases.</p>
intervention type	Intervention type is a broad category referring to the entomological effect and use pattern of an intervention. Multiple intervention classes may fall under the umbrella of a single intervention type.
pesticide	Any substance, mixture of substances, microorganism (including viruses) or biological agent intended for repelling, destroying or controlling a pest. Targets include vectors of human or animal disease, nuisance pests, and unwanted species of plants or animals that are causing harm or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feed stuffs. Pesticides may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term also includes substances intended for use as insect or plant growth regulators; defoliants; desiccants; agents for setting, thinning or preventing the premature fall of fruit; and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport. Pesticide synergists and safeners, where they are integral to the satisfactory performance of the pesticide, also come under this term.
prequalification	Prequalification for vector control interventions is WHO's standardized assessment procedure for evaluating the acceptability, in principle, of vector control products for purchase by United Nations agencies. Agencies using the information resulting from the prequalification procedure should perform additional assessment prior to purchasing, such as verifying the supplier's financial stability, standing and ability to supply the required quantities; ensuring the security of the supply chain; and evaluating pre-shipment quality control and other related aspects.

product amendment	A product amendment is a change in the specification of an active ingredient and/or a formulation (including source of materials), labelling, production process or manufacturing site of a prequalified product; any amendment must be submitted to WHO for review.
product claim	A product claim is information contained in the product's label and advertisement materials. For vector control products, this includes the product's chemical content (where appropriate); target arthropod vector; entomological effect in controlling target vectors or protecting against infection and/or disease; duration of effect; and role in mitigating insecticide resistance, etc.
product class	A product class in vector control is a group of products that share a common entomological effect by which it reduces pathogen transmission and thus reduces infection and/or disease in humans. For products in a class not currently recommended by WHO, efficacy trials with a first-in-class product must generate epidemiological evidence of protective efficacy against infection and/or disease. The evidence is then reviewed by VCAG to validate the public health value of the product class. This validation forms the basis of a WHO recommendation for the new product class.
product label	The written, printed or graphic matter on or attached to the vector control intervention or its immediate container, as well as the outside container or wrapper of its retail package.
product life cycle	This refers to the period of time that the product is on the market until it is withdrawn from the market. The management of the product life cycle includes the applicant's continual updating of product information (formulation, labelling, production sites and manufacturing processes) to WHO. A product that has been withdrawn or delisted has effectively ended its life cycle, and there will be no further maintenance of the product's prequalification.
public health value	A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.
use patterns	A use pattern of a vector control intervention is the way in which an intervention is applied to control the vectors. This may not apply to all types of interventions because they can only be used in a single manner. Examples of different use patterns for the same intervention might be the application of an insecticide for space spraying to control adult mosquitoes and to water bodies to control immature mosquitoes.
vector control product	A vector control product is any tool designed to reduce infection and/or disease caused by a vector-borne pathogen through control of the disease vector.

Study designs

case-control study	This type of study compares the prevalence of an exposure (for example, the use of a protective intervention) between a group of people with the disease of interest (cases) and a group of people without the disease (controls). In a study of this type, the controls should be selected so that they are representative of the case population as much as possible.
cluster randomized controlled trial (CRCT)	A cluster randomized controlled trial is a study in which groups of individuals (for example, a household, village, geographical area, or administrative unit) are randomly allocated to receive either an intervention treatment or the control.
cohort study (observational)	This is a type of observational study in which groups of disease-free individuals are identified, who are either 'exposed' (they use the protective intervention) or 'unexposed' (they do not use the protective intervention). The groups are then followed over a period of time to evaluate the outcome of interest (usually disease or infection). In this study type, individuals are not allocated to the intervention of interest by the investigators.
cohort study (randomized)	This is a randomized controlled trial in which a cohort of recruited individuals is randomized to receive either the treatment intervention or control intervention. The cohorts are followed up for the outcome of interest for a specified period.
control group	This is the group of participants that receives no intervention, a placebo or the current standard of care (depending on the study design), and this group thereby serves as a comparison group when the intervention results are evaluated.

cross-sectional study	In an analytical cross-sectional study, information is collected at one point in time on the prevalence of the outcome of interest (for example, a disease or infection) and exposure (for example, the use of a protective intervention).
controlled before & after study	A study in which observations are made about an intervention both before and after the implementation of an intervention in both the treatment (intervention) group and a control group (that does not receive the intervention). This is also known as a pre-post study.
crossover study	A study in which individuals or clusters are allocated to the intervention or control group for a period of time before switching (or crossing over) to the other group. There is usually a washout period before the switch is made to avoid carry-over effects from the intervention.
effectiveness study	These studies estimate the effect of an intervention under pragmatic (or real-life) conditions (for example, interventions delivered under routine conditions) so that the relevance of the findings for WHO recommendations and practice is maximized.
efficacy trial	These studies estimate the effect of an intervention under the ideal conditions that can usually be achieved only in a trial, for example, by ensuring maximal coverage of the target population and adherence to the intervention.
interrupted time series	This is a type of study in which the outcome (for example, disease incidence) is measured on a number of occasions, both before and following the introduction of an intervention. This allows an investigator to determine whether an intervention has had an impact greater than any underlying trend in the data. This design may include a parallel control group.
non-inferiority study	A non-inferiority trial aims to demonstrate that the tested product is not worse than the comparator by more than a small, pre-specified amount, which is known as the non-inferiority margin (δ). The difference between the effect of the test product (T) and the effect of the comparator (C) must be less than δ – that is, the upper bound of the 95% confidence interval of C – T must be less than δ . The choice of δ is a clinical (or entomological) judgement, not a statistical one. The smaller the δ , the less T is inferior to C, but the larger the required sample size.
observational study	This is a type of study in which the effect of the exposure on the participants is observed, but the investigator has no role in assigning participants to the exposure.
randomized controlled trial (RCT)	In this study design, individuals are randomly allocated to either the intervention or control group. The intervention and control groups are then followed up for the outcome of interest for a specified period.
stepped-wedge design	This is a type of study in which the intervention is rolled out to different clusters in a staged fashion. At the end of the study, all clusters will have received the intervention. The order in which clusters receive the intervention is usually determined at random.
test-negative case-control study	This is a type of case-control design wherein the use of an intervention is compared between cases who test positive and those who test negative (controls) who present to a health facility. The advantage of this design is that cases and controls are recruited in a single step and there is no need to spend time testing individuals to identify controls from the community.
time series study	In this type of study, the outcome (for example, the incidence of disease) is measured on a number of occasions following the introduction of an intervention. Typically, measurements are made at equally spaced time points, for example, monthly or yearly. In some cases, there may also be a control time series of people who have not received the intervention, in which the same measurements are made, although some time series studies do not have a control group.

ANNEX 2. ROLES AND RESPONSIBILITIES

PATHWAY STEP	OUTCOME	TASK	INPUTS	OUTPUTS	APPLICABLE TO		APPLICANT	WHO			
					PRODUCT WITH WHO POLICIES	PRODUCT WITHOUT WHO POLICIES		PQT -VCP	GMP	NTD	VCAG
Determination of pathway	Evaluation pathway determined by WHO Pre-submission Coordination Committee (PCC)	Convene meeting with applicant to field process enquiries on the determination of pathway process	Pre-submission enquiry	Clarity on requests for determination of pathway	X	X	I	R,A	C	C	
		Submit pre-submission package to PQT-VCP (pqvectorcontrol@who.int)	Cover letter, completed request for determination of pathway, and draft product label	Addition to agenda for next PCC	X	X	R,A	I			
		Screen pre-submission package	Pre-submission package	Potential request for clarification	X	X	C	R,A			
		Convene PCC meeting to determine appropriate evaluation pathway	Pre-submission package; other information	PCC conclusion on appropriate pathway	X	X	I	R,A	C,A	C,A	
		Communicate PCC meeting conclusions to applicant	PCC conclusion on appropriate pathway	Correspondence sent to applicant	X	X	I	R,A	I	I	
Evaluation of vector control tool, technology or approach	Dossier submitted	Submit dossier to PQT-VCP	Product dossier	Logged application	X	X	R,A	I			
	Dossier screened	Screen dossier for completeness	Product dossier	Acceptance for assessment, request for information, or failure	X	X	I,C	R,A			
	Safety assessment	Conduct human health assessment	PQ dossier - Module 4	Data evaluation records (DERs), risk assessment, discipline summary	X	X		R,A	I	I	
	Environmental assessment	Conduct environmental assessment (depending on product type)	PQ dossier - Module 4	DERs, risk assessment, discipline summary	X	X		R,A	I	I	

R = Responsible, A = Accountable, C=Consulted, I= Informed

PATHWAY STEP	OUTCOME	TASK	INPUTS	OUTPUTS	APPLICABLE TO		APPLICANT	WHO			
					PRODUCT WITH WHO POLICIES	PRODUCT WITHOUT WHO POLICIES		PQT -VCP	GMP	NTD	VCAG
Evaluation of vector control tool, technology or approach (cont.)	Quality assessment	Carry out physical/chemical and manufacturing assessment	PQ dossier - Module 3	DERs, draft specification, discipline summary	X	X		R,A	I	I	
		Develop specifications through JMPS process	Module 3, DERs, draft specification	Final specification	X	X	I	R,A	I	I	
	Entomological efficacy assessment	Provide advice on entomological data requirements and test procedures to manufacturers	Tools without policy: PQT-VCP works with applicants (or another group) to devise appropriate and reliable indicators of quality and efficacy	Guidance on entomological data requirements and test procedures provided to applicant		X	I	R,A	C,I	C,I	
			Tools covered by policy: Enquiry from manufacturer and submission of data package as part of dossier		X		I	R,A	C,I	C,I	
		Develop/update evaluation criteria/thresholds to assess entomological efficacy	Advice provided to manufacturers of new tools and/or new evidence on evaluation methods	New evaluation criteria/ thresholds established or existing ones modified	X	X		R,A	C	C	
		Develop/update testing guidance	Advice provided to manufacturers of new tools and/or new evidence on evaluation methods	Efficacy test guidelines	X	X		R,A	C	C	
		Conduct entomological efficacy assessment	PQ dossier - Module 5	DERs, Discipline Summary to	X	X	I	R,A	I	I	

PATHWAY STEP	OUTCOME	TASK	INPUTS	OUTPUTS	APPLICABLE TO		APPLICANT	WHO			
					PRODUCT WITH WHO POLICIES	PRODUCT WITHOUT WHO POLICIES		PQT -VCP	GMP	NTD	VCAG
Evaluation of vector control tool, technology or approach (cont.)	Assessment of public health value (i.e. epidemiological efficacy)	Review preliminary entomological data from laboratory & small scale field studies to inform epidemiological trial designs	Preliminary entomological data as submitted by applicant	Feedback on preliminary entomological data provided to applicant via WHO		X	I	R,A	C	C	I
		Develop protocol for epidemiological studies	Guidance as provided in trial design manual and, tailored to specific interventions, in VCAG reports	Draft study protocol		X	R,A	I	I	I	I
		Review draft protocol for epidemiological studies	Draft protocol	Guidance on study design to applicant		X	I		R,A	R,A	R
		Finalize study protocol	Updated protocol	Final VCAG endorsed study protocol		X	R,A		I	I	I
		Initiate epidemiological efficacy studies	VCAG endorsed study protocol	Data package from epidemiological trials, incl. data analysis by applicant		X	R,A	I	I	I	I
		Carry out periodic review of study progress	Investigator update to VCAG	Technical advice to applicants		X	I		R,A	R,A	R
		Assess public health value based on the data generated	Data analysis as conducted by investigator. Independent analysis of raw data may be required.	VCAG recommendation to GMP and NTD (MPAC and STAG) regarding public health value		X	I	I	R,A	R,A	R
	Label review	Review labelling based on outcomes of reviews of Modules 3,4,5	Declaration of Labelling (included in dossier submission)	Declaration of Labelling	X	X	C	R,A	I	I	
	Inspection	Inspect manufacturing/ production facilities to ensure compliance with WHO-recommended quality standards	PQ dossier - Module 6 (Site Master Files)	Inspection report(s)	X	X	C	R,A	I	I	

PATHWAY STEP	OUTCOME	TASK	INPUTS	OUTPUTS	APPLICABLE TO		APPLICANT	WHO			
					PRODUCT WITH WHO POLICIES	PRODUCT WITHOUT WHO POLICIES		PQT-VCP	GMP	NTD	VCAG
Evaluation of vector control tool, technology or approach (cont.)	Policy recommendation for programmatic use	GMP / NTD develops WHO policy recommendation with support of a WHO Guideline Development Group	VCAG recommendations regarding public health value communicated to WHO	WHO policy recommendation and establishment of new product class, as communicated by means of updated guidelines document		X	I	I	R,A	R,A	I
Product prequalified	Product listed on PQT website	PQT-VCP prequalifies product based on assessment of product efficacy, safety and quality and outcomes of site inspection	Decision document	Product and related information included on the WHO PQT-VCP website	X	X	I	R,A	I	I	
Communications	VCAG outcomes communicated	Establish and maintain clear communication with applicants	Submission of application to VCAG Secretariat	Meeting reports, direct communication with applicants.		X	I	C	R,A	C	
	Product prequalification communicated	Regularly update and publish list of prequalified products	Decision Document	Product listing	X	X	I	R,A	I	I	
	Policy recommendations and deployment guidance communicated	Conduct webinars; disseminate guidance through regional meetings and other communications opportunities	Updated WHO guideline document. For malaria, all guidelines will be available via MAGICapp from January 2021.	Updated guidelines shared with vector control community through various channels	X	X	I	I	R,A	R,A	

ANNEX 3. CRITERIA FOR USE OF EVIDENCE TO INFORM RECOMMENDATIONS IN WHO GUIDELINES

Guidelines Review Committee guidance (16 March 2019)

Background

World Health Organization (WHO) guidelines contain one or more recommendations which are informed by a comprehensive, systematic review of the relevant evidence on benefits and harms of an intervention or effects of exposure on priority outcomes. In addition, recommendations are informed by evidence on other important considerations that may modify the successful implementation and impact of the recommendations in various contexts.

Decisions on the inclusion of types of evidence for specific recommendations are based on the underlying principles of evidence-informed decision-making, which are, in turn, based on the principles of scientific rationale.¹

Principles

These principles underpin all decisions to include or exclude particular study designs, individual studies, or data from specific sources from the body of evidence that informs a recommendation.

1. All WHO guidelines must be developed based on sound scientific and ethics principles and practices and must meet the highest international standards.
2. The evidence that is used to inform a WHO recommendation should be:
 - a. relevant (applicable to the key question(s) at hand),
 - b. obtained ethically and in accordance with human rights standards and ethics;²
 - c. of the highest quality ("best") available (based on an assessment of the risk of bias); and
 - d. publicly-available at the time of publication of the recommendation or guideline.
3. The choice of specific study designs will vary depending on the question, the amount of evidence available, and factors related to the risk of bias and applicability of the study design to the question at hand.
4. The type of guideline will impact on the comprehensiveness of the retrieval, the assessment of the evidence, and the choice of restrictions on date and language of publication (e.g. guidelines produced in response to a public health emergency may require modified approaches but in no case shall exceptions to 2(b) be permitted).
5. WHO guidelines must be transparent with respect to the sources for evidence; methods for searching, retrieving, summarizing and assessing the evidence used to inform recommendations; and the rationale for decisions on selected approaches and methods, and for each recommendation must be clear.
6. All conflicts of interest among any contributor to primary data and studies, to evidence synthesis and appraisal, or to guideline development must be disclosed and significant conflicts of interest managed.
7. WHO and its staff have a responsibility to promote and support the highest quality of data generation, research, evidence synthesis and guideline production. To that end, WHO has a critical role in promoting and facilitating research study registration; publication of research and systematic review protocols; data sharing and transparency; optimal reporting of

1 Scientific rationale entails three domains: the "episteme" (knowledge), the "phronesis" (practical wisdom), and the "techné" (technique or know-how to do). De-Regil LM 2008 (Scientific rationality, causality and metaanalyses of clinical trials. *Salud Publica Mex* 2008;50:523–529).

2 Universal Declaration of Human Rights and Bioethics Art 6(2) (3), WHO Guidance on ethics of research in emergencies (2015).

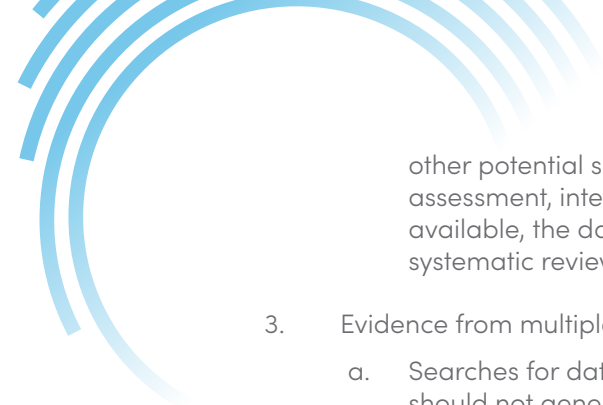
datasets, research studies and guidelines; publication of all research studies and all results; and identification of gaps in knowledge and guidance to inform future research and guidelines including attention to redressing gender and other biases in research and reporting.

Policy for WHO staff who develop guidelines

This policy outlines the general approaches for establishing criteria for inclusion of various types of evidence and their sources to inform recommendations in WHO guidelines. It does not provide detailed guidance on the methods for identifying, appraising and presenting evidence.

The body of evidence informing questions or recommendations in a WHO guideline includes:

1. All types of study designs as appropriate to the question(s) underlying a recommendation and according to other relevant considerations.
 - a. For questions on the benefits and harms of interventions, high-quality randomized controlled trials (RCTs) addressing the question provide the highest quality evidence with regards to causality and potential confounding. However, RCTs may not be available, may be unethical or infeasible, or may have significant limitations, including for example, inclusion of highly selected populations which may not be representative of the populations to which the recommendation is intended to be applied.
 - i. Thus, non-randomized study designs including experimental designs (e.g. quasi-randomized trials and investigator-assigned cohort studies) as well as observational studies (e.g. before-after or parallel-group cohort studies or surveillance data) may be included in the body of evidence to inform benefits and harms. Case studies or case series may be included in selected situations.
 - b. For questions related to considerations other than benefits and harms of an intervention (e.g. feasibility, equity, acceptability, resource use), the best available evidence should be used and the choice of specific study designs will vary depending on the question and other factors.
 - c. Regardless of study design, risk of bias needs to be assessed using a tool appropriate for a given study design. Sufficient information must be available to permit this assessment and assessments must be performed by persons who are independent of the data or studies (i.e. have no significant conflicts of interest).
 - d. Studies at significant risk of bias, either considered as a group according to study design, or according to assessments of individual studies, can be explicitly excluded using pre-defined, explicit and evidence-based criteria. However, excluding individual studies based on assessments of risk of bias must be done carefully as such assessments are a judgement and the criteria can be debated. A common approach is to perform a sensitivity analyses around various criteria, rather than using them as exclusion criteria.
2. Primary data, research studies or systematic reviews
 - a. All relevant evidence should be included, whether primary data (raw data, individual-patient data), data from research studies, results from mathematical modelling studies, or existing or newly commissioned systematic reviews. Data and studies can be quantitative, qualitative or encompass mixed-methods approaches.
 - b. The criteria for including data and studies in the evidence base used to inform each specific recommendation within a guideline are developed according to the relevant considerations for that question or recommendation. These criteria include but are not restricted to: study design considerations, potential confounders and



other potential sources of bias, the nature of the review question (e.g. prognosis, risk assessment, intervention effect, impact on health equity), the amount of evidence available, the date of the data collection in a study or the date of searching for a systematic review, and feasibility and timelines for guideline production.

3. Evidence from multiple sources

- a. Searches for data and study results should be tailored to the research question and should not generally be restricted to those indexed in bibliographic databases.
- b. Data and studies accessible in all languages should be considered for inclusion.
- c. Searches should encompass clinical trial registries such as the WHO International Clinical Trials Registry platform (ICTRP, <http://apps.who.int/trialsearch/>) when the evidence base may include RCTs. Other sources should be examined as appropriate, for example local programmatic data and evaluations, and pre-publication data shared by investigators with the expectation that at least a summary of the methods and results will be made publicly available no later than the time of publication of the recommendation or guideline.
- d. Databases, publication sites, predatory journals, or other sources that are not deemed credible or trustworthy should not be used as sources for evidence.
- e. All included evidence regardless of source must be evaluated for risk of bias and the highest quality evidence should be used to inform recommendations.
- f. Study results that may be preliminary such as those presented at conferences or in meeting abstracts can be included on a case-by-case basis after careful assessment of their nature, likelihood that they might change, and risk of bias. The use of any data, whether summary results or primary data, that may be deemed preliminary must be done with extreme caution, after discussions with the principle investigator(s) and with careful consideration of the benefits versus potential downsides of their use.

4. Publicly available evidence

- a. The methods and results of research used to inform a recommendation in a WHO guideline must be publicly available to the reader/end-user at the time of publication of the guideline. Throughout the guideline development process, WHO staff should make this requirement explicit to all relevant parties.
- b. Both published and unpublished data and studies should be considered equally as part of the evidence base used to inform a WHO recommendation.
 - i. The terms “published” and “unpublished” data and studies (or evaluations) are inexact and variably defined, and publication status does not correlate with quality or trustworthiness of data or studies. Herein we define published data or studies to be those where the information is reproduced in an indexed journal or in a monograph from an established publisher. Publicly-available means that the data or studies are available in print or online to the public, whether free or for a fee, irrespective of whether they are indexed in a bibliographic database.
 - ii. An important resource providing access to unpublished data is the summary results section of clinical trials registries. Results disclosure in such registries is legally required in many jurisdictions including United States and the European Union and is WHO’s official position.³
- c. If for some reason the data or studies cannot be made accessible at the time of publication of a WHO guideline, the WHO Steering Group for the guideline, in collaboration with the (external) Guideline Development Group and WHO senior management in the technical unit producing the guideline need to carefully weigh

³ WHO Statement on Public Disclosure of Clinical Trial Results, available at <https://www.who.int/clinical-trials-registry-platform/reporting-on-findings> (accessed 11 February 2019) .

the risk to the Organization and to global public health of using these data versus not using them. Note the following options and considerations:

- i. A summary of the data or study can be made available on a WHO or other web-site which is freely accessible to the public in the situation where full access to the data or to detailed summary study results is not possible.
- ii. If the data owner will not agree to make the study results or a summary thereof publicly available at the time of publication of the WHO guideline, at a minimum WHO must provide a list of the studies and/or datasets that were included in the assessment on a publicly available web-site, and highlight those that were not released into the public domain by the interested party. WHO should indicate that all efforts were made to seek permission to make the results publicly available and for which studies this permission was denied and by whom. This is not an optimal approach as it limits accessibility and transparency, however it does provide some level of transparency on what information was used by the Guideline Development Group to make its decisions, and it allows other interested parties to seek access to these data to verify the findings.
- iii. The original (raw) dataset does not have to be made publicly available; a synthesis of the results will suffice.
- iv. If the data owner shares study results with a WHO Guideline Development Group for the purposes of informing a recommendation, but will not make the study results available publicly in any way (including in summary form or as part of a systematic review) by the date that WHO releases the guideline, the WHO guideline will name the principal investigator and data owner and indicate that they refused to permit public disclosure of the study results at the time of publication of the WHO guideline. A citation as a personal communication should be included. The guideline may present sensitivity analyses including and excluding these data as indicated.
- v. If the principal investigator or data owner refuses to share study results with WHO for the purpose of informing a recommendation in a guideline, the WHO guideline will name the principal investigator and data owner and indicate that they did not share the study results with WHO to inform a specific recommendation or guideline.



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