World Health Organization

# WHO handbook for guidelines development

## Supplement. Criteria for use of evidence to inform recommendations in World Health Organization guidelines

**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 type of 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. emergency interim guidelines produced in response to a public health emergency may require modified or abbreviated 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;

[1] Scientific rationale entails three domains: the "*episteme*" (knowledge), the "*phronesis*" (practical wisdom), and the "*techne*" (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).

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 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 of effectiveness, 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.
    b. 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.
    c. 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.
    d. 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).
    e. 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, https://www.who.int/clinical-trials-registry-platform) 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. All included evidence regardless of source must be evaluated for risk of bias and the highest quality evidence should be used to inform recommendations.
    e. 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 preliminary and non-peer reviewed data has grown exponentially following the outbreak of COVID-19 in 2020, with many journals now providing free access to pre-print servers. ICMJE has recently published guidance on appropriate standards for preprint publishing, that include a clear description of a journals pre-print policy, clear citation of pre-prints and careful selection of preprint archives. Evidence cited from such sources should adhere as much as possible to this guidance.
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 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.



[3] WHO Statement on Public Disclosure of Clinical Trial Results, available at Reporting on findings (who.int) (accessed 29 March 2023).