



# **WHO Information Note on developing policy guidance for drug- resistant tuberculosis**

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# WHO Information Note

## on developing policy guidance for drug-resistant tuberculosis

### Background

Providing evidence-based guidelines to inform public health service delivery for Member States and other stakeholders is one of the core responsibilities of the World Health Organization (WHO).

WHO guidelines are typically tailored for clinical and programmatic management of diseases and other health conditions, rather than for managing individual patients through personalised medicine practices. The perspective of WHO guidelines is global and recommendations aim to be adaptable to a broad range of public health contexts worldwide.

This Information Note outlines the WHO rules and procedures that govern our policy mandate to ensure transparent, independent, accurate, and scientifically sound [guidelines and policy documents](#)<sup>1</sup> for the comprehensive management of drug-resistant tuberculosis (TB) which, by its nature, requires complex clinical and public health interventions.

This Information Note also clarifies the role and target audiences of [supportive documents \(information and implementation products\)](#) to WHO guidelines using specific examples. These documents are developed through long-standing collaborations, both across WHO and with external partners.

### Guidelines and Policy documents

WHO guidelines and policy documents are those **containing recommendations** for clinical practice or public health policy, derived from independent and scientifically sound evidence.

WHO guidelines and policy document advise intended end-users what to do in specific circumstances to achieve optimal public health outcomes, including selection and prioritization across a range of potential interventions where indicated.

WHO develops four main types of guidelines to best fit the intended purpose.<sup>1</sup> These are:

- **Standard guidelines**, which cover a specific clinical or policy area (e.g. the use of an existing medicine in the treatment of drug-resistant TB). These guidelines may vary in scope and focus and recommendations are either developed *de novo* or by updating existing/previous WHO guidelines;
- **Consolidated guidelines** which compile all recommendations from existing WHO guidelines on a specific topic (e.g. the treatment of drug-resistant TB). Producing consolidated guidelines is complex because individual recommendations may become outdated at different times given newly emerging scientific evidence;
- **Interim guidelines** which are produced when WHO is asked to provide guidance on newly emerging or incomplete/limited data (e.g. the use of a new medicine in treatment of drug-resistant TB);
- **Guidelines in response to an emergency or urgent need** which are produced when WHO is asked to provide guidance in response to either public health emergencies (emergency or rapid response guidelines); or when there is uncertainty about what to do in a specific situation; or after the release of breakthrough data (rapid advice guidelines, WHO position statements, WHO policy briefs).

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<sup>1</sup> The [WHO Handbook for Guideline Development](#). Readers are also encouraged to consult the webpage of the [WHO Guidelines Review Committee](#), which oversees all WHO guidelines development.

All currently valid WHO guidelines and policy recommendations for TB (including those for diagnosis and treatment of drug-resistant TB) are contained in one consolidated [WHO Compendium](#). In 2018 the Compendium will be released as an application for mobile devices to facilitate further access to WHO policies.

A single page for WHO TB guidelines has been created on our web page to facilitate online searches for guidelines of interest: <http://www.who.int/publications/guidelines/tuberculosis/en/>.

## Implementation and information products

Developing recommendations for drug-resistant TB is complex given the nature of the disease, the limitations of current tools (including diagnostics), the impact of underlying epidemics (especially HIV) and the low quality of evidence usually available given the paucity of clinical trial data.

Managing drug-resistant TB poses many health service challenges (including transmission and infection control; patient support to facilitate treatment adherence and reduce patient costs; ethics and human rights) as well as treatment-specific challenges (including medicine dosing; off-label medicine use, management of toxicity; and drug-drug interactions). Many of these issues are critical to proper programmatic roll-out.

WHO has therefore developed extensive supportive documents to our formal policy guidelines in order to provide the necessary 'how-to' advice for their implementation. These complement the evidence-based recommendations contained in guidelines.

Links to WHO implementation and information products for managing drug-resistant TB are provided in the [WHO Compendium](#). Specific examples below illustrate the breadth and scope of such documents, tailored towards specific end-users:

**Implementation frameworks** consolidating conceptual, programmatic approaches for implementation of WHO-recommended interventions/technologies for drug-resistant TB, are usually focused on emerging issues and are also intended for subsequent integration into implementation documents:

WHO [Framework for active tuberculosis drug safety monitoring and management](#)  
Guiding countries on how to establish pharmacovigilance activities for new TB medicines.

WHO [Policy Framework for implementing new tuberculosis diagnostics](#)  
Guiding end-users on selection of diagnostics at different levels of laboratory services.

**'How-to' documents** providing detailed implementation considerations for drug-resistant TB interventions/technologies recommended by WHO and serving as technical reference documents for programmatic and clinical purposes:

WHO [Companion Handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis](#)  
Providing detailed advice on the practical aspects of care delivery, including diagnostic and treatment algorithms, drug administration and dosing, monitoring, and management of adverse drug reactions.

WHO [Handbook for the use of digital technologies to support tuberculosis medication adherence](#),  
Supporting WHO evidence-based recommendations on digital technologies in TB care delivery.

**Best-practice statements** aiming to provide consistent and suitable approaches to emerging challenges faced by clinicians and programmes in delivering drug-resistant TB care:

WHO [Best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis \(MDR-TB\)](#)

Supporting clinicians and national programmes to take individual decisions on the use of these two medicines beyond their authorized indication.

**Position statements** providing updated information about WHO-recommended interventions in light of the release of additional results, usually in response to stakeholder requests:

[WHO position statement on the use of delamanid for multidrug-resistant tuberculosis](#), following an expedited review of the phase III clinical trial data of delamanid added to an optimised background MDR-TB regimen.

[WHO position statement on the continued use of the shorter MDR-TB regimen](#), following an expedited review of the STREAM Stage 1 preliminary results.

**Frequently-asked questions** summarising the most common questions from end-users on drug-resistant TB interventions/technologies recommended by WHO. The content of these documents are eventually incorporated into subsequent updates of implementation documents:

[Frequently asked questions](#) about the implementation of the 2016 WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions;

[Frequently-asked questions](#) on molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs;

[Frequently-asked questions](#) on the non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF.

**Technical reports** reflecting the outcomes of specific technical expert meetings or technical task forces convened by WHO to address issues of emerging public health concern or where global consensus on specific technical aspects are desirable. These documents do not contain recommendations but provide relevant technical background to inform eventual WHO guidelines:

WHO [Technical Report](#) on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis;

WHO [Technical Report](#) on pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis;

WHO [Technical Report](#) on the non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF.

**Fact sheets** summarising the most recent drug-resistant TB approaches/technologies recommended by WHO or the most recent global data on drug-resistant TB reported to WHO and contained in the annual WHO Global TB Report:

[Fact Sheet on molecular line probe assays](#) for the detection of resistance to second-line anti-TB drugs;  
[Fact Sheet on the shorter MDR-TB regimen](#);  
[Fact sheet on multidrug-resistant TB](#) from the annual Global TB Report.

## Guideline development: processes and procedures

Like many leading institutions globally, WHO has adopted the international [GRADE](#) process (Grading of Recommendations, Assessment, Development and Evaluation) for scientific evidence assessment and development of evidence-based policy guidelines and recommendations.

GRADE ensures the highest standards for an independent review of evidence, identification and mitigation of bias and a structured, transparent approach to derive policy recommendations. It is facilitated by [online tools](#) for guideline developers.

WHO recommendations using GRADE are governed by the rules of the WHO Guideline Review Committee (GRC) and based on a systematic and comprehensive assessment of the quality of scientific evidence, balance of benefits and harms, considerations of equity and human rights, end-user values and preferences, feasibility, acceptability and resource implications (see below).

### Timing of guidelines

WHO develops or updates guidelines whenever there is a solid evidence base for a public health intervention, relevant new developments or specific needs expressed from stakeholders, most notably our Member States.

The technical departments in WHO responsible for guidelines development, therefore, continuously track the scientific literature and are in close contact with scientists, national programmes, technical implementers, donors and other stakeholders to ensure that emerging evidence and public health needs are addressed in a timely fashion.

Standard WHO guidelines typically have a life-cycle of three to five years; however, new evidence or need for guidance from end-users may result in more frequent updates of these guidelines or the release of interim or rapid response guidelines (including WHO position statements, see above).

### Selecting Guideline Development Groups

The development of WHO guidelines is conducted through a Guideline Development Group (GDG), selected according to specific criteria described in the [GRC Handbook](#). GDGs are convened according to the relevant topic and scope of the anticipated guidelines.

GDG members are selected to reflect a broad range of multi- and interdisciplinary stakeholders encompassing the required technical and clinical knowledge, programmatic experience, geographic and gender representation. First and foremost, we focus on the needs of persons and communities likely to be affected by the interventions, expressed through the voices of (preferably) former drug-resistant TB patients or nominated civil society representatives (e.g. from the WHO/Global TB Programme (GTB) Civil Society Task Force).

### Managing declarations and conflicts of interests

Managing declarations of interest (DOIs) is critical to the credibility and trustworthiness of WHO policy recommendations. The WHO guideline development processes are designed to minimize risk of bias and conflicts of interest (COI) affecting the independence of GDG members.

The methods for managing conflicts of interest are explicitly defined in the GRC Handbook and the handling of COI is overseen by the WHO Office of Compliance, Risk Management and Ethics.

COI considerations include both financial and non-financial issues, including intellectual conflicts. The latter is particularly challenging. Intellectual conflicts such as public declarations of firm opinions against or in favour of interventions to be assessed by WHO, or professional/personal affiliation with organizations advocating for or against products or interventions ahead of review of the evidence pose a specific risk, as described in the GRC Handbook.

Potential GDG members are screened and vetted according to WHO rules. This process includes an examination of financial contributions received by individuals or their respective employers or family members, as well as written or oral opinions publicly expressed for or against any interventions being considered by WHO.

**Individuals with financial or intellectual conflicts cannot be appointed to GDGs.** This aspect is particularly relevant to advocacy groups, where a fine line exists between responsible advocacy for a well-established intervention and active lobbying in favour of or against a specific intervention targeted for WHO guideline development or update.

Individuals with specific technical expertise yet declared interests (e.g. systematic reviewers, data contributors, individuals with unique technical skills) may be included in our GDG meetings as technical resource persons and/or observers, provided that relevant interests are known to WHO and the GDG members. Technical resource persons and observers are, however, restricted from participating in the development of actual WHO recommendations, as per WHO and GRC rules.

As implementation and information products are derivative documents of WHO guidelines, participation of external technical experts or other interested individuals are more flexible (although contingent upon exclusion of COI). Many external partners, implementers and other stakeholders have been involved in the production of the derivative documents listed above, contributions that have enriched these resources and which is much valued and appreciated by WHO.

## Formulating the guideline questions

The formulation of questions to inform WHO guidelines consists of two types of questions:

- **Background questions** provide context and rationale for the proposed guideline. They pertain to important background information on the issues under consideration and their context. They do not relate to evidence of the type that directly informs recommendations but lead to information to frame and formulate the foreground question.
- Typical background questions in the drug-resistant TB context relate to the prevalence, burden and distribution of disease; the pathophysiologic mechanisms underlying exposure or disease transmission; pharmacological properties of second-line medicines and the effects of dosage on therapeutic/toxic levels; or definitions for treatment outcomes. Answers to background questions come from a wide range of information sources, including surveillance data, basic scientific or pharmacological data, frameworks explaining behavioural change or technical reports (such as those listed above).

- **Foreground questions** directly inform and underpin WHO recommendations, as outlined in the GRC Handbook. For diagnostic tests, the key questions usually revolve around sensitivity, specificity, positive and negative predictive values and other related parameters such as cost and cost-effectiveness. For treatment interventions, the key questions usually pertain to the efficacy, effectiveness and potential harms of the intervention, as well as to factors such as acceptability, feasibility, the values and preferences of those who will be affected by the recommendations and cost and cost-effectiveness (see below).
- Foreground questions are formulated in **PICO format**, an acronym capturing the four elements that need to be considered in any question governing a systematic search of the evidence. These are **P**opulation, **I**ntervention (or exposure), **C**omparator (e.g. standard of care, placebo, no intervention) and **O**utcome. For example, a typical question in PICO format in the context of drug-resistant TB is “Among different groups of MDR-TB patients (**P**), does the inclusion of drug X (**I**) to the WHO-recommended regimen (**C**) improve the cure rate at 24 months (**O**)?”
- The GRC Handbook advises that PICO questions be crafted in a simple, clear format that includes the four essential components, followed by a detailed list of inclusion and exclusion criteria for the body of evidence that will be used to answer the key question (see below). In the context of drug-resistant TB, several separate PICO questions are often required to provide the evidence base for WHO recommendations, as outlined in the respective guidelines.
- The scope of the guidelines and the draft PICO questions are proposed by WHO to the GDG. The GDG decides on the final list of questions, their wording, the prioritization of subgroups and the ranking of outcomes. The GDG may change, drop and add questions based on priority areas of debate and controversy in any particular aspect of drug-resistant TB care.

### Commissioning evidence retrieval and synthesis

- **Systematic reviews** of the scientific literature underpin all WHO recommendations. If conducted properly, systematic reviews reduce the risk of bias and improve the accuracy and reliability of conclusions based on evidence.
- GRC rules stipulate that systematic review teams commissioned by WHO must have demonstrated expertise in using GRADE and should produce GRADE evidence profiles. The systematic review teams involved in evidence retrieval and assessment for WHO drug-resistant TB guidelines all follow international standards set by the [Cochrane Collaboration](#); comply with [PRISMA](#) reporting standards for systematic reviews; and use internationally recognized management software to search and organize reference libraries used in these reviews.
- Methods employed in search strategies for WHO guidelines involve unique aspects such as the inclusion of specific searches for studies from low- and middle-income countries in all six WHO regions; searches for evidence in WHO’s six official languages; searches for grey literature (studies not indexed in commercial bibliographic databases); unpublished data; and data from study registries (such as the international [Clinical Trials Registry Platform](#) sponsored by WHO and which includes the US-based [ClinicalTrials.gov](#)).
- **Meta-analysis** of data where feasible is another core component of evidence synthesis for WHO guidelines, as is the use of **individual patient data** (IPD) analyses based on [Cochrane](#) international principles.

- Pooled IPD analyses have been useful to inform the current WHO drug-resistant TB guidelines, given the complexity of regimen design and the paucity of data from randomised controlled clinical trials and large-scale cohort studies.
- IPD databases for patients treated for drug-resistant TB (longer and shorter MDR-TB regimens, isoniazid-resistant TB) are maintained by McGill University, Canada. WHO periodically contracts McGill University to update the databases and undertake IPD meta-analyses to inform guideline revisions. Methods followed are in accordance with international standards for IPD analysis and analysis plans are agreed beforehand with data contributors.
- Some of the most frequent applications of IPD analyses for drug-resistant TB relate to assessing the relative contributions of individual medicines for designing MDR-TB treatment regimens, the duration of treatment and the impact of drug susceptibility testing profiles on treatment outcomes.
- In the beginning of 2018 WHO issued a [public call](#) inviting countries and technical partners to share their data in preparation of the 2018 update of our drug-resistant TB treatment guidelines. As a result of this call, the data available for IPD analyses to inform the 2018 drug-resistant TB guidelines will be supplemented by anonymized individual data from clinical trials, cohort/observational studies and programmatic implementation.

## Developing recommendations

### Quality of the evidence

In the context of guideline development based on GRADE, the **quality/certainty of evidence** reflects the confidence that specific estimates of effect are adequate to support a particular recommendation. Factors that influence the quality of the body of evidence are described in detail in the GRC Handbook. GRADE categorises the quality of the evidence as outlined in Table 1.

**Table 1.** Certainty of evidence in GRADE

Quality level	Definition
<b>High</b>	High confidence that the true effect is close to the estimated effect
<b>Moderate</b>	Moderate confidence that the true effect is likely close to the estimated effect, but there is a possibility that it is substantially different
<b>Low</b>	Limited confidence in the estimate of effect; the true effect may be substantially different from the estimate of effect
<b>Very low</b>	Very little confidence in the estimate of effect; the true effect likely to be substantially different from the estimate of effect

### Strength and direction of recommendations

Detailed descriptions of the factors that guide the formulation of WHO recommendations are outlined in the GRC Handbook.

The main factors determining the **strength and direction of recommendations in GRADE** are: (i) the certainty/quality of the evidence; (ii) values and preferences related to the outcomes of an intervention (or exposure); (iii) the balance of benefits and harms; and iv) resource implications.

Resource implications are never the main driver of WHO policy guidelines for drug-resistant TB. Nevertheless, end-users of WHO guidelines (notably national programmes and donors) often enquire

about cost, affordability and value for money of WHO-recommended interventions, given that not all countries can immediately afford all possible public health interventions in their health budgets.

Several other factors are highly relevant when formulating public health, health system and health policy recommendations. These include the importance of the problem being addressed, equity and human rights, acceptability and feasibility.

In the context of guideline development based on GRADE, the strength of a recommendation expresses the degree to which the GDG is confident in the balance between desirable and undesirable consequences of implementing the intervention as a public health measure. Recommendations are therefore defined as ‘strong’ or ‘conditional’ as outlined in Table 2.

**Table 2.** Interpretation of strong and conditional recommendations for an intervention

Target audience	Strong recommendation	Conditional recommendation
<b>Patients</b>	Most would want the intervention; only a small proportion would not and decision aides not likely to be necessary	Most would want the intervention, but many would not;
<b>Clinicians</b>	Most individuals should receive the intervention	Different choices will be appropriate for individual patients; decision aides likely to be necessary
<b>Policy-makers</b>	The recommendation can be adopted as policy in most situations	Policy-making will require substantial debate and involvement of various stakeholders

- **Strong recommendations** in drug-resistant TB guidelines are relatively uncommon (similar to many other public health situations), as the balance between benefits and harms of implementing individual recommendations is rarely certain. It is particularly challenging to make strong recommendations on evidence for which the quality is low or very low.
- **Conditional recommendations** in drug-resistant TB guidelines are therefore relatively common but often misunderstood by end-users. A conditional recommendation does not mean that end-users should refrain from implementing the recommendation; rather, it describes the conditions under which end-users should (or should not) implement such a recommendation.
- Uptake of conditional WHO recommendations in national HIV and TB guidelines has showed that such recommendations are frequently adopted, albeit less frequently than strong recommendations.<sup>2</sup>

### Implementing and disseminating guidelines and associated information products

As outlined above, we are consistently addressing the needs of implementers for detailed practical advice as part of our guidance development activities. This is done by investing significant time and resources into development of implementation tools in collaboration with key stakeholders, including individuals from non-state actors and civil society. Much appreciation for and extensive use of these tools are consistently expressed by end-users.

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<sup>2</sup> [Nasser, Syed Muhammad Umar et al. Strength of recommendations in WHO guidelines using GRADE was associated with uptake in national policy. Journal of Clinical Epidemiology, Volume 68, Issue 6, 703 – 707.](#)

Capacity building for disseminating and implementing our guidelines takes place via much-valued partnerships and global mechanisms. These include the Working Groups of the Stop TB Partnership for which WHO provides the Secretariats (GDI, Global Drug-Resistant TB Initiative; GLI, Global Laboratory Initiative, PPM, Public-Private Mix; and the Childhood TB Working Groups); technical partners such as USAID, KNCV, MSF and The Union; as well as the regional GLC network across all WHO regions.

## Striving to optimise and improve our processes and procedures

- WHO standards for guideline development and GRC oversight ensure the integrity of our processes and generate trust by end-users.
- In order to avoid misunderstanding on existing normative products and the role of accompanying documents (e.g. implementation guidance), we plan to pursue further consolidation of guidelines as needed, standardise the terminology for the various information products and provide clear definitions and target audiences.
- Over the past few months we have consulted with several Member States; key stakeholders; the WHO GRC; the WHO Office of Risk Management, Compliance and Ethics; and the WHO Legal Department. Two major findings are highlighted:
  - From the perspectives of the internal bodies governing and overseeing WHO guideline development, the process followed by GTB is regarded as fully transparent, high-quality, inclusive, and respectful of the rules of the Organization.
  - Guidelines for drug-resistant TB produced by WHO/GTB are considered - by Member States, technical implementers and donors - as being highly responsive to emerging evidence and to their respective needs.
- We have established formal collaborations with regulatory authorities and other global agencies developing guidelines, notably the American Thoracic Society, the US Centers for Disease Control and Prevention, and the Infectious Disease Society of America, to jointly conduct systematic reviews and be mutually represented on GDGs. This limits duplication of efforts and enables individual agency guidelines to be explicit about specific recommendations and reasons why these may differ from those of WHO.
- We are strengthening mechanisms for communication and dissemination of our policy guidance documents by harnessing digital tools; intensifying stakeholder briefings; accelerating training and capacity development throughout the WHO network; and optimising opportunities for knowledge sharing during international and local conferences and workshops.