Frequently Asked Questions (FAQs) – July 2023

Application to add MS disease-modifying therapies (DMTs) on the World Health Organization (WHO) Essential Medicines List (EML)

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Definition of terms

Disease-modifying therapy (DMT): DMTs are medicines that aim to prevent or reduce the number of relapses that occur, as well as slowing down the overall progression of the disease. DMTs are not a cure for MS. DMTs are different from medicines used to manage relapses or symptoms of MS, e.g. pain.

Follow-on product: Medicines are referred to as 'follow-on' products if they are based on and made after the original drug that was developed (i.e. once the patent has expired). They may also be referred to as generic or biosimilar medicines.

Off-label DMT: A medicine is used 'off-label' when the drug has regulatory approval for a different disease or indication, but not the one being treated. The use of some medicines off-label is very common in clinical practice. The evidence-base for off-label use varies between different medicines and indications. Off-label DMTs are often more readily available and affordable in health systems.

World Health Organization (WHO) Essential Medicines List (EML)

1. What is the WHO EML and why did MSIF apply for multiple sclerosis disease-modifying therapies (DMTs) to be added onto the WHO EML?

Data from the Atlas of MS show that people with MS in 70% of countries face barriers in accessing disease-modifying therapies (DMTs). Improving access to MS treatments globally has been prioritised by MSIF and its members, as a key aim in our strategy.

The World Health Organization's (WHO) Essential Medicines List (EML) has a critical role in improving access to medicines globally. The EML aims to be a guide for decision-makers – including Ministries of Health – on which medicines should be available as a minimum in all health systems. This makes it a key tool to support advocacy activities at the national level. In the 2021 WHO EML very few medicines for neurological conditions were included on this list – and there are none listed for MS. Listing MS DMTs on the WHO EML creates a tool for awareness-raising and advocacy regardless of whether a country has an effective national EML or not. It is a WHO-level stamp of approval, moving the conversation from whether MS DMTs should be made available to how to make them available. Importantly, the listing of any MS DMTs on the WHO EML will formally acknowledge MS as a global health concern, and put it higher on the agenda of the WHO and individual countries.

MSIF applied for MS treatments to be added to the EML in 2018, working closely with the World Federation of Neurology and all regional TRIMS networks. The WHO Expert Committee did not

recommend the addition of the medicines, but recognised the public health need for effective and affordable treatments for MS and requested a revised application.

Since 2019, MSIF has been working with collaborators and partners to develop a revised application, which was submitted to the WHO in December 2022. The WHO Expert Committee decided to list MS DMTs on the WHO EML, which was announced in July 2023.

2. Which MS DMTs were listed on the 2023 WHO EML and who made this decision?

In July 2023, the WHO announced that the application to add MS DMTs on the complementary list of the WHO EML was successful. A new section for multiple sclerosis was added under 'Medicines for diseases of the nervous system', and rituximab, cladribine and glatiramer acetate were included as individual medicines.

Rituximab is an anti-CD20 medication, administered by infusion, that has been used off-label in the treatment of MS for more than two decades. In low-resourced settings, rituximab offers several advantages. It is highly efficacious and suitable across a broad range of disease presentations, including paediatric MS. While currently contraindicated during pregnancy, women's MS experts around the world have used rituximab to provide effective disease management alongside careful family planning. Emerging data also suggests safety during breastfeeding. Rituximab is already listed on the WHO EML, is widely available and listed on many national EMLs, and has a lower price across different income settings.

Cladribine is an oral medication for the treatment of RRMS and active SPMS in adults. Cladribine offers several advantages in low-resourced settings, as it requires only 16-20 days of total treatment distributed over 2 years, and further treatment is not needed for at least another two years. This significantly reduces the likelihood of treatment disruptions in settings where medication supplies can be erratic. While it is contraindicated to use cladribine during pregnancy and breastfeeding, it may be used to plan around pregnancies given its infrequent dosing. Limitations in low-resourced settings include that people with HIV and TB, as well as pregnant and breastfeeding women and men and women of childbearing age who do not have access to reliable contraception, cannot use this therapy.

Glatiramer acetate is a treatment for RRMS administered by subcutaneous injection. Glatiramer acetate offers several advantages in low-resourced settings, including its lack of monitoring requirements, good safety profile without risk of opportunistic infections, and safety in women of childbearing age, pregnant and breastfeeding women, and paediatric populations (it is now licensed for paediatric use and has been used off-label in clinical practice in paediatric MS for many years). The major drawbacks to its use in these settings are its non-preferred administration route (i.e. injections) and its refrigeration requirement.

The application to add MS DMTs on the WHO EML was a joint application between MSIF and the WHO Collaborating Centre Bologna. The DMTs selected were selected by an international, multi-disciplinary panel, using rigorous GRADE methodology and systematic reviews by the Cochrane group of all MS DMTs. The application was endorsed by 15 global and regional MS research and clinical networks (TRIMS) and neurological academies. Please see Question 8 for further details on the methodology.

All applications are assessed by the WHO Expert Committee at a meeting on 24-28 April 2023 at WHO headquarters in Geneva. Members of the Expert Committee are selected from WHO Expert Advisory Panels based on their professional expertise and experience, representing practical experience from all regions of the world and across all levels of national income. The application received three expert reviews in favour of the application, a letter and statement in support from Clinton health Access Initiative (CHAI) and a letter from the Institute for Clinical and Economic Review (ICER). The WHO Department of Mental Health and Substance Use also supported the application.

The Executive Summary of the meeting can be found here and the full document with the updated EML list will be released in September/October 2023.

3. Three MS DMTs have been listed on the WHO EML, but there are many more treatments for MS. Is it possible to apply for more MS DMTs to be added on the WHO EML?

The WHO EML is open to applications to add or remove medicines every two years. Applications can be submitted by anyone – an individual, organisation or company. While there are no limits to the number of medicines that can be added, the WHO EML is priority list, aiming to identify what is needed for a baseline of care. It is not an exhaustive list of all medicines that are effective and important for the treatment of MS. Applications to add more MS DMTs are possible in the coming years.

It is important to note that in a national setting, a country may choose to make available a larger number or different MS DMTs than those listed on the WHO EML, depending on the local context. It will be important to ensure a range of options are available and that high efficacy DMTs are included.

4. Now that the MS DMTs are added on the WHO EML, will this automatically improve access to MS DMTs?

No, this is only the beginning. The WHO EML has several important functions.

Firstly, it acts as a **guide for national EMLs**. These are often updated by the national ministry of health every 2-5 years, depending on the country. National advocacy is needed for local neurologists and decision-makers to ensure MS DMTs are included in the national EMLs and careful consideration is given to which DMTs are most appropriate for their national setting.

Secondly, this decision is a **WHO stamp of approval.** Listing MS DMTs on the WHO EML is an important signal to different entities within the health system (e.g. regional decision-makers, non-communicable disease programmes, procurement systems, hospital formularies) to ensure MS DMTs are available and affordable, and that MS is treated promptly and appropriately. Local action and advocacy by health systems, healthcare professionals and the MS community is needed to ensure access to MS DMTs is improved.

Lastly, many **international organisations**, including the WHO, require medicines to be listed on the WHO EML in order to be prioritised within their work. For example, the Medicines Patent Pool

negotiates voluntary licenses for patented medicines listed on the WHO EML to accelerate access to affordable quality treatments. Pharmaceutical companies also tend to be more willing to consider special access and licensing arrangements for treatments listed on the WHO EML.

5. Are the DMTs listed on the WHO EML the only ones that are effective for MS? The DMT I am on is not listed, what does this mean? Will my health system/insurance stop providing other DMTs to people with MS?

No, we are not stating that the DMTs proposed for the WHO EML are the only ones appropriate for treating MS. The WHO EML listing should not affect individuals who are currently treated with a DMT, other than potentially widening their choice of treatments. These individual decisions should only be made between the person with MS and their healthcare professional.

It would be a misinterpretation of this WHO EML application for health providers/systems to restrict access to other DMTs currently provided in the country.

The selection of the proposed DMTs was based on the process outlined in Question 8, and the application emphasises that this recommendation should not be interpreted as the only appropriate and necessary DMTs to treat MS. The proposed DMTs are a recommendation of **the most essential MS DMTs** that should be available in all health systems at all times. It is important to note that the WHO EML acts as a guide for national decision-makers, and the local situation may influence which DMTs are most appropriate for that setting. The listed DMTs each offer unique advantages and are particularly relevant in low-resource settings and provide a critical base of effective MS treatment.

6. Some of the treatments listed are very expensive in my country, how can access to these be improved?

Cost and affordability of DMTs has been highlighted as one of the main barriers to accessing DMTs in the Atlas of MS. Our WHO EML application research showed that the price of DMTs varies greatly between countries, for various reasons. Getting accurate price information is also challenging as negotiated prices between health systems and pharmaceutical companies are often under non-disclosure agreements.

Listing treatments on the WHO EML creates momentum and opportunities for making DMTs more affordable and available across different income levels. Immediate pathways to affordability are improved by market concentration in low-resource settings, tiered pricing, effective negotiations, co-ordinated and pooled negotiations and procurement activities. Companies often have access schemes to ensure essential medicines are available and affordable, including in low-resource settings.

In the long term, increased demand stimulates the development of follow-on products. Follow-on products create a more competitive landscape, which can lead to lower-priced medicines. Quality biosimilar and generic products are already available for a number of DMTs. No follow-on products are available for cladribine, but other options can be explored, e.g. voluntary licensing.

7. How can I use the WHO EML to advocate for improved access to MS DMTs in my country?

Questions 4 and 6 outline some of the opportunities for advocacy associated with the decision for MS to be recognised by WHO by listing MS DMTS on the WHO EML. For effective national advocacy efforts, it is important to have a good understanding of the key paths for influencing change, and an effective network of stakeholders and potential collaborators. Decision-makers also appreciate systematically collected evidence on the number of people with MS and their current access to DMTs in the country. Clear, professional communication plays an important role, as well as showing the lived experience of people with MS in your country. MSIF is developing advocacy tools in the coming years to support local advocacy efforts, which you can find on our website: https://www.msif.org/access-to-ms-healthcare/

Please contact us for template letters, press releases, slides and speaking opportunities on access@msif.org.

Selection of MS DMTs put forward by MSIF and the WHO Collaborating Centre (CC) Bologna onto the WHO EML

8. How did MSIF and WHO CC Bologna decide which MS DMTs to put forward onto the WHO EML? Which other DMTs were considered?

For the WHO EML application submitted in 2022, the WHO EML Secretariat gave us very detailed guidance about what they expected in terms of rigorous evidence reviews of MS DMTs. We were also asked to include both licenced, on-label DMTs and off-label DMTs. All identified MS DMTs were assessed: 30 different medicines in total.

MSIF convened two independent panels, whose members underwent a rigorous conflict-of-interest assessment by independent organisations. The first panel systematically reviewed evidence (in the form of randomised and non-randomised controlled studies) for two off-label DMTs, azathioprine and rituximab. These two DMTs were specifically mentioned by the WHO as requiring consideration in the review process, and they are also the most commonly used off-label DMTs, according to data from the Atlas of MS. The second panel reviewed evidence and ran a network meta-analysis for all 30 MS DMTs, based on randomised controlled trials (RCTs) only.

MSIF partnered with the Cochrane MS group and McMaster GRADE Centre during this process, both groups being internationally regarded as experts in the field of evidence reviews and decision-making.

The recommendations – focusing on DMTs in low-resource settings – from the two independent panels were combined, resulting in a shortlist of 3 DMTs to be included in the EML application.

The decision took into account the following factors:

- Balance of clinical benefits and harms
- Certainty of the evidence
- Cost and cost-effectiveness in low-resource settings
- Values, equity, acceptability, feasibility and availability (particularly in low-resource settings)
- The needs of special populations – pregnancy, breastfeeding and paediatric MS

9. Who was on the MSIF Essential Medicines Panel?

This MSIF Essential Medicines Panel is an international multi-stakeholder panel, which included people affected by MS from Uruguay, Morocco, Serbia and Namibia. All six WHO world regions were represented; 19 countries, 48% from Upper-Middle (UMIC) or Lower-Middle Income Countries (LMIC). The gender balance was also considered with 60% female and 40% male representatives. As the panel focused on DMTs relevant for treating MS in low-resource settings, the panel included neurologists from sub-Saharan Africa, Western Pacific, South East Asia and Latin America.

10. Which organisations endorsed the application?

We have consulted with global and regional MS research and clinical networks (TRIMS) and neurological academies.

The following organisations have endorsed the application:

- World Federation of Neurology (WFN)
- African Academy of Neurology (AFAN)
- Indian Academy of Neurology (IAN)
- European Academy of Neurology (EAN)
- American Academy of Neurology (AAN)
- Neurology Society of Ghana (NSG)
- Neurological Association of Zambia (NAZ)
- Nigerian Society of Neurological Sciences (NSNS)
- Neurological Society of Kenya (NSK)
- Neurology Association of South Africa (NASA)
- Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS)
- Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (PACTRIMS)
- Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS)
- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)

11. Why was cladribine proposed and not one of the other oral DMTs, e.g. fingolimod or dimethyl fumarate? Cladribine is very expensive and not widely available in my country/region. Affordable follow-on products of fingolimod and dimethyl fumarate are available in my country/region.

Fingolimod, dimethyl fumarate and cladribine are all effective DMTs, and were carefully considered by the panel for the WHO EML application. It is not feasible to propose all DMTs suitable for treating MS, and the panel had to recommend only a small number of prioritised DMTs. We are not saying cladribine is the only DMT that is needed or relevant, and acknowledge that in some countries fingolimod or dimethyl fumarate may be more practical options. Countries are free to consider which DMTs should be listed on their national list, depending on the local context, barriers and opportunities. The WHO EML is a *model list* that can be adapted to the local situation.

Cladribine was recommended due to the short treatment regimen, low monitoring and pre-test requirement, and low risk of rebound disease activity in case of disrupted medicine supply. Dimethyl fumarate and fingolimod were both discussed at length by the panel. The long-term use and gastro-related adverse events of dimethyl fumarate, and the additional pre-tests, monitoring and risk of rebound disease activity associated with stopping fingolimod, led the panel to recommend cladribine. Many countries face disrupted medicine supply for various reasons, so rebound risk was considered an important issue.

Cladribine is not available and affordable in some countries, and the aim of the WHO EML listing is to improve access. Once listed, different options are possible to advocate for improved affordability, these include voluntary licensing, in-country price negotiations, and pooled negotiations or procurement.

12. Why was glatiramer acetate proposed for inclusion? It is not used in some world regions, people with MS do not like injections and many clinicians prefer to use higher efficacy DMTs. Why was interferon not proposed, as it is often considered very similar to glatiramer acetate?

It is not feasible to propose all DMTs suitable for treating MS, and the panel had to recommend only a very restricted number of prioritised DMTs. We are not saying glatiramer acetate is the only DMT that is needed or relevant, and acknowledge that in some countries or circumstances, another DMT may be a better choice. Countries are free to consider which DMTs should be listed on their national list, depending on the local context, barriers and opportunities. The WHO EML is a *model list* that can be adopted to local situation.

Glatiramer acetate has very low monitoring and pre-testing requirements, and a good safety profile during pregnancy. MS is more common in women, and the age of onset of MS means that pregnant women a relevant special population to take into account. Unplanned pregnancies may also be common in low-resource settings and WHO emphasises women's health as one of its priorities. In some countries glatiramer acetate is approved for use with paediatric MS.

The decision about whether to recommend interferon or glatiramer acetate was discussed at length by the panel. Glatiramer acetate was recommended based on the following arguments: better safety data for pregnancy than interferon; less monitoring required; more tolerable (interferon's flu-like side effects were considered worse). The limitations of obtaining originator glatiramer acetate in some world regions, due to political issues, was also mentioned. As there are now follow-on products that would be more acceptable even in these regions, it was considered to be a changing landscape.

13. Rituximab is used to treat other diseases, but does not have regulatory approval for MS and is considered 'off-label'. Why was it proposed for inclusion on the WHO EML?

While rituximab does not have regulatory approval for multiple sclerosis, it has been used off-label in the treatment of MS for more than two decades. It may offer a moderate to large benefit, compared with a range of other medicines, in preventing relapses in MS. In some countries, off-label use of rituximab is common and is also reimbursed. For example, around 50% of people with MS in

Sweden use rituximab; Norway included rituximab in their health technology assessment for MS; British Columbia in Canada includes it in their limited coverage drugs for MS; and Kaiser Permanente Southern California includes rituximab among treatments under experimental use for MS. MSIF's off-label treatments (MOLT) panel reviewed all published, controlled evidence for rituximab in MS and recommended use of rituximab in settings where a range of DMTs are not accessible.

The panel noted that rituximab is a feasible and acceptable option in low-resource settings due to balance of effects; mode of administration (6-monthly infusions); and low maintenance for screening and monitoring. It has a low risk of rebound effect if treatment is discontinued, and there are low discontinuation rates by people with MS. Rituximab, while contraindicated during pregnancy, may be used with careful timing of treatment. Rituximab has been extensively used off-label to treat paediatric MS.

Rituximab is already listed on the WHO EML for other indications, is off-patent with many follow-on products authorised, and part of the WHO prequalification program.

On-label ocrelizumab is more costly than off-label rituximab, but the panel decided to propose ocrelizumab in the WHO 'square box grouping'. This means ocrelizumab is indicated as a therapeutic alternative, which is important because in some countries off-label prescribing and reimbursement is very difficult. This would provide flexibility depending on an individual country's situation. However, the WHO Expert Committee decided not to include ocrelizumab in the square box listing on the WHO EML due to the high price and more restricted availability compared to rituximab.

14. Does listing on the WHO EML mean that rituximab will get regulatory approval for an MS indication?

For rituximab to get regulatory approval for MS, or become 'on-label', an organisation, usually a pharmaceutical company, would need to apply to a regulatory authority for the MS indication to included. This would most likely need expensive clinical trials to be completed for MS. As rituximab is not under patent in many countries, there are limited financial incentives for pharmaceutical companies, so this is unlikely to happen.

There are some very new pathways for regulatory approval to be granted based on real-world evidence of off-label use and/or without a pharmaceutical company required to be the applicant. Such schemes have been used at least once by the US Food and Drug Administration (FDA) to add a paediatric indication for a drug, and the European Medicines Agency (EMA) has started a pilot program on repurposing of authorised medicines. The UK also has a scheme to repurpose medicines without specific marketing authorisations.

15. Why were other anti-CD20 therapies (ocrelizumab, ofatumumab, ublituximab) with regulatory approval not listed on the WHO EML? Should off-label rituximab access and use be prioritised over other anti-CD20 therapies?

As outlined in Question 8, all MS DMTs were included in the initial assessment by the panel for the 2023 WHO EML application. Rituximab was proposed in the application together with ocrelizumab in the 'square box' grouping. Ofatumumab and ublituximab were not included in the square box

grouping in this application. Ofatumumab has a different mode of administration and was not prioritised for the full EtD analysis. Ublituximab has now completed phase III trials, but the results were published after the systematic review was conducted. Future consideration of whether they should be proposed in the square box grouping is needed.

The WHO Expert Committee decided to only list rituximab and not to include ocrelizumab in the square box listing on the WHO EML due to its high price and more restricted availability compared to rituximab.

We are not suggesting rituximab is the only anti-CD20 DMT that is effective or relevant, or that rituximab is more effective or safer than other anti-CD20 products. The panel used 13 EtD criteria to select the proposed medicines, including equity, feasibility, accessibility, availability, cost and cost-effectiveness. Rituximab was found to have a consistently lower cost than ocrelizumab across different settings, it was more available, it is already listed on the WHO EML for other indications, it is off-patent with quality follow-on products already authorised, and is part of the WHO prequalification program.

Rituximab is recommended when **a range of DMTs are not accessible** by both the MOLT panel and MEMP. This should not be interpreted as 'when no other DMTs are accessible' or 'when no on-label DMTs are accessible', as there are circumstances where some on-label DMTs are available, but they may not be the best option for the person with MS. Rituximab compared favourably to a number of other treatments even when only considering clinical benefit and harm, so there may be circumstances where it is the best treatment choice for people with MS.

We acknowledge that in some countries other anti-CD20 products may be more appropriate. Countries are free to consider which DMTs should be listed on their national list, depending on the local context, barriers and opportunities. The WHO EML is a model list that can be adapted to the local situation.

16. Why was azathioprine not put forward? It is very cheap and available in most countries.

Azathioprine lacked sufficient clinical evidence to warrant proposal at this stage, because there have only been limited studies in very small populations. However, those small studies did indicate that azathioprine could be an effective treatment, so more research, including higher quality and larger studies, would provide greater certainty on the potential benefits and harms. If more evidence emerges, azathioprine could be re-evaluated for inclusion.

Please note that MSIF's off-label treatments (MOLT) panel recommended azathioprine when no other treatment choices are available, i.e. when the alternative is no treatment.

Methodology: GRADE, certainty of evidence ratings and evidence-to-decision framework

17. Why did the panel use GRADE for grading the certainty of evidence and the evidence-to-decision framework? It does not seem sensitive enough to consider evidence for MS, many GRADE certainty ratings are low or very low?

GRADE methodology is applied to both the grading of evidence and to the evidence to decision framework. GRADE is an internationally recognised, systematic way of assessing evidence that has been broadly used by guideline development organisations since it was developed in 2001. It is now used by over 110 organisations, including the World Health Organization and European Commission. GRADE methodology is developed by the GRADE Working Group (https://www.gradeworkinggroup.org/), an open and international network with over 500 members. The evidence to decision framework provides a rigorous structure for guideline panels to consider a range of criteria that are important to all healthcare decision makers, including, in this case, people with MS.

We used GRADE methods for the MOLT and MEMP guidelines to ensure a transparent and structured approach for reviewing evidence. GRADE is also recommended and often requested by international organisations, e.g. WHO, and national health systems, e.g. NICE in the UK. It is important to separate the judgement on **certainty of evidence** from the wider judgements involved in making **guideline recommendations**. The evidence-to-decision framework element of GRADE had particular relevance to our application to the EML due to the common ground between the framework's criteria and the WHO's criteria for reviewing EML applications. Taking an evidence-based approach to each of the criteria in the framework meant we assembled all the evidence the WHO would need to make their decision.

Certainty of evidence

Certainty of evidence is one of the criteria of the evidence-to-decision framework. Central to GRADE methodology is distinguishing the strength of the recommendation (strong or conditional, in favour or against an intervention) and the certainty of the evidence that this recommendation is based on. GRADE certainty is expressed in four levels: very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), and high (⊕⊕⊕⊕). GRADE is based on the consideration of a body of evidence's design. Randomised control trials are initially rated as high certainty and observational/non-randomised studies as low certainty, unless they are rated as low risk of bias with ROBINS-I, in which case they also begin as high certainty. Subsequently, grading considers rating down the certainty of evidence in the following domains:

1. **Risk of bias** – Assessed using the Risk of Bias Tool (https://www.riskofbias.info/), including the ROBINS-I tool for non-randomised controlled studies (https://www.bmj.com/content/355/bmj.i4919). This domain will consider if the trial was randomised and blinded appropriately, if there was loss of follow-up of participants, and in case of an observational study, if the analysis was adjusted for important cofounders.
2. **Inconsistency** – This is assessed by whether confidence intervals overlap, point estimates of effects are considerably different, and whether formal tests and measures show statistical heterogeneity.
3. **Indirectness** – Considers whether the studied intervention is the exact intervention of interest in terms of dosing, mode of administration etc.
4. **Imprecision** – This domain is assessed on whether the effect is compatible with benefits and harms, if there are few participants and/or observed events in the included studies, i.e. wide confidence intervals of the overall effect.
5. **Publication bias** – Considers whether only small studies that confirm investigators perception of the effects of an intervention are available, and whether additional studies were conducted but not published.

And if there are no issues, an outcome could then be rated up if applicable in the following domains: dose-response effect, large effect and opposing plausible bias. This may increase confidence in the certainty of evidence.

Each **outcome** is assessed for certainty of evidence. The overall rating for the PICO question is determined by the **lowest certainty of a critical outcome**:
https://www.jclinepi.com/article/S0895-4356(12)00025-X/fulltext

Other considerations (e.g. lack of reproducibility or number of studies in the evidence review), have been thoroughly assessed by the GRADE Working Group, and are either already a part of one of the aforementioned domains or deemed not to affect the certainty of evidence.

Evidence-to-Decision framework

Certainty of evidence is only one of the criteria used in the evidence-to-decision framework. The full list of criteria is used by the panel to make the recommendations using a multi-comparison of all the criteria for each DMT.

Evidence-to-Decision criteria used for the MEMP guidelines and WHO EML application:

1. Is the problem a priority?
2. How substantial are the desirable anticipated effects?
3. How substantial are the undesirable anticipated effects?
4. What is the overall certainty of the evidence of effects?
5. Is there important uncertainty about or variability in how much people value the main outcomes (values)?
6. Does the balance between desirable and undesirable effects favour the intervention or the comparison?
7. How large are the resource requirements (costs)?
8. What is the certainty of the evidence of resource requirements (costs)?
9. Does the cost-effectiveness of the intervention favour the intervention or the comparison?
10. What would be the impact on health equity?
11. Is the intervention acceptable to key stakeholders?
12. Is the intervention feasible to implement?
13. What is the regulatory status, market availability, and availability of pharmacopoeial standards for this medicine?