Frequently Asked Questions (FAQs) – January 2023

Guidelines for the use of essential medicines for the treatment of MS in low-resource settings

Table of Contents

Definitions 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.

Essential medicines

1. What are essential medicines, and why is MSIF making recommendations?

Data from the Atlas of MS shows 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.

Essential medicines are those that should be available as a minimum in all health systems. Many countries have national 'essential medicines lists' considering which medicines should be prioritized with limited availability and budget restraints. MSIF analysed the WHO database of national essential medicine lists (Laurson *et al.* 2021, Table 1), and found that off-label MS DMTs were listed more often than on-label MS DMTs. This prompted a consideration of which MS DMTs should be made available in all health systems. The MSIF guidelines of essential medicines for MS considered all on-label and off-label DMTs identified to be used for MS.

National essential medicines lists often consider the model World Health Organization's (WHO) Essential Medicines List (EML). Currently, very few medicines for neurological conditions are included on the WHO EML, none are listed for MS. These MEMP guidelines were considered together with MSIF's Off-Label Treatments (MOLT) guidelines to propose MS DMTs on the World Health Organization essential medicines list in December 2022.

The MEMP recommendations on essential medicines for MS should work as a guide for decision-makers, including ministries of health, to consider if MS DMTs should be listed nationally, and which MS DMTs should be considered. MS organisations and other health advocates may use these recommendations to provide evidence-based rationale for making MS DMTs available in all health systems.

2. When the guidelines for essential medicines for MS are published, will this automatically improve access to MS DMTs?

No, this is only the beginning. These guidelines provide evidence-based recommendations that MS DMTs are essential and guidance on which MS DMTs should be made available. To improve access to MS DMTs, strong advocacy efforts are needed on a national level to influence decision-makers.

These recommendations provide 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.

The recommendations also highlight the importance of treating MS with effective DMTs. They signal to different entities within the health system (e.g. regional decision-makers, non-communicable disease programmes, procurement systems, hospital formularies) that MS DMTs should be available and affordable, and that MS is treated promptly and appropriately. Local action and advocacy by healthcare professionals and the MS community is needed to ensure access to MS DMTs is improved.

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

No, we are not stating that the recommended DMTs are the only ones appropriate for treating MS. These recommendations should not affect individuals who are currently treated with a DMT. These individual decisions should only be made between the person with MS and their healthcare professional.

It would be a misinterpretation of these guidelines for health providers/systems to restrict access to other DMTs currently provided in the country.

The recommendations were based on the process outlined, and the guideline emphasises that these recommendations should not be interpreted as the only appropriate and necessary DMTs to treat MS. The recommendations highlight **essential MS DMTs** for low-resource settings.

4. Some of the treatments recommended 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 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.

Considering medicines 'essential' often creates momentum and opportunities for making DMTs affordable and available for everyone, regardless of where they live. 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 these medicines are available and affordable also 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, resulting in lower-priced medicines. Quality biosimilar and generic products are already available for a number of DMTs. No follow-on products are available for some of the medicines, but other options exist, e.g. voluntary licensing.

5. How can I use the essential medicines guidelines to advocate for improved access to MS DMTs in my country?

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. These guidelines provide evidence-based recommendations for essential medicines for MS – making the case that MS treatments *are essential* and providing guidance on *which DMTs should be considered*. 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 will be developing advocacy tools in the coming years to support local advocacy efforts.

Recommendations of essential medicines for MS

6. How did MSIF decide which MS DMTs to recommend in the guidelines? Which DMTs were considered?

MSIF convened an independent panel, whose members underwent a rigorous conflict-of-interest assessment by an independent organisation. The panel reviewed evidence and ran a network meta-analysis for all MS DMTs, based on randomised controlled trials only. All identified MS DMTs were assessed: 30 different medicines in total.

MSIF partnered with the Cochrane MS group and McMaster GRADE Center during this process, both groups being internationally regarded as experts in the field of evidence reviews and decision-making. The panel used the GRADE Evidence-to-Decision (EtD) framework for relapsing forms of MS and progressive forms of MS. The full EtDs, including evidence, judgments and panel discussion, can be accessed here.

The recommendations took into account the following factors:

- Balance of benefits and harms
- Certainty of the evidence
- Cost and cost-effectiveness in low-resource settings
- Values, equity, acceptability, feasibility and availability in low-resource settings

7. Who is on the MSIF Essential Medicines Panel?

This MSIF Essential Medicines Panel is an international multi-stakeholder panel, which included people affected by MS from 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.

8. What does a 'either for or against' recommendation mean?

'Either for or against' recommendations are neutral recommendations, that are dependent on the setting. The recommendations are made for 'low-resource' settings, but the panel noted that these settings have a large amount of heterogeneity in the infrastructure and services available. A number of medicines received 'either for or against' recommendations due to feasibility of pre-tests, monitoring requirements, cost and affordability, limiting the application of these DMTs in some low-resource settings. The panel felt a recommendation for or against these medicines for low-resource settings was appropriate, despite evidence of significant clinical benefit. Importantly, the panel noted that in settings where the testing and monitoring requirements can be met reliably and where cost is not a barrier, these treatments have an important role to play.

9. Rituximab does not have regulatory approval for MS and is considered 'off-label'. Why is it recommended as an essential medicine?

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 and may offer moderate to large benefit against a range of other medicines in preventing relapses in MS. In some countries, off-label use of rituximab is common and reimbursed. For example, around 50% of people with MS in Sweden are on 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 evidence for rituximab in MS, and recommended rituximab 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 low discontinuation rates by people with MS. Rituximab is also listed on the WHO EML for other indications, is off-patent with many follow-on products authorised, and part of the WHO prequalification program.

10. Why was azathioprine recommended only with an 'applicable remark' of situations where nothing else is available? It is very cheap and available in most countries.

Azathioprine lacked sufficient clinical evidence to warrant a 'for' recommendation with limited studies in very small populations. However, those studies did show a potential benefit for azathioprine, so more research, including higher quality and larger studies, would be beneficial. If more evidence emerges, azathioprine could be re-evaluated.

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

11. When you say 'affordable', what does it mean?

Affordability is relative and depends on a number of factors, e.g. the price, budget available and the time-frame of treatment (acute vs chronic). There are both direct treatment costs (price of medicine) and indirect treatment costs (associated tests, equipment, time with healthcare professional, training or storage). The indirect costs may differ between different DMTs, but all on-label and off-label DMTs will have some indirect costs associated. The price of the medicines varies widely and the information is rarely available and transparent. The research team collated data on the price of DMTs. The analysis can be found in the EtDs.

Our recommendations are conditional on other DMTs not being available and affordable, or accessible. This is in recognition that many instances, DMTs are available in theory, e.g. they are registered for use by the local regulatory agency, but people can't afford to buy them. In many low- and middle-income countries and low-resource settings, all (or a large proportion) of the medicine's cost is paid by the person with MS. Many health insurance systems do not cover MS as a disease, chronic medication, high-cost medicines or MS DMTs in general. The price difference between DMTs can make MS treatment either impossible or possible.

Our stakeholders have raised concerns that health insurance providers may switch to cheaper DMTs, e.g. azathioprine, due to very low cost on the premise that other DMTs are not 'affordable', even if they are available. It would be a mis-interpretation of these guidelines to limit access on the premise of cost. Off-label use of DMTs to treat MS should be driven by the need to protect the person's health.

Furthermore, as the recommendations are unambiguous in that azathioprine should be considered only when no other DMTs are available and affordable, health systems should strive to provide other DMTs to improve health outcomes for people with MS. Azathioprine alone is not an adequate treatment option to provide for MS, and should only be considered when no other alternatives exist.

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

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

GRADE methodology is an internationally recognized, systematic way of assessing evidence that has been broadly used by guideline development organizations since its advent in 2001. It is now used by over 110 organisations, including the World Health Organization and European Commission. GRADE methodology is advanced by the GRADE Working Group (https://www.gradeworkinggroup.org/), an open and international network with over 500 members.

We used GRADE 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 judgment on **certainty of evidence** from judgments of **guideline recommendation**.

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 controlled 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 our confidence in the certainty of evidence.

When making guideline recommendations, the exact question is formulated as a 'PICO question'. This way of formulating the question ensures the Population, Intervention, Control and Outcomes are clearly defined.

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.