Frequently Asked Questions (FAQs) – updated March 2022

MSIF Off-Label Treatments (MOLT) Panel

Guideline for the use of off-label azathioprine and rituximab for the treatment of multiple sclerosis in low-resource settings

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Scope of the guidelines and the MOLT panel

1. Why are these guidelines for off-label DMTs being developed?

   The need for guidelines for off-label DMTs has been outlined in our recent publication: "*Ethical use of off-label disease-modifying therapies for multiple sclerosis*" https://journals.sagepub.com/doi/full/10.1177/13524585211030207

   The use of off-label DMTs in MS is common, reported from at least 89 countries. There is a need for structured and transparent evidence-based guidelines to support clinical decision-making, pharmaceutical policies and reimbursement decisions for off-label DMTs. MSIF set up an independent panel to address this need.

2. Why are guidelines being developed for azathioprine and rituximab? Why do the guidelines not consider other off-label DMTs, e.g. leflunomide and (non-oral) cladribine?

   The methodological approach to review evidence and develop guidelines can be used to review any off-label DMTs. The methods are outlined in our recent publication: *"Multiple Sclerosis International Federation guideline methodology for off-label treatments for multiple sclerosis"* https://journals.sagepub.com/doi/10.1177/20552173211051855

   We chose azathioprine and rituximab to pilot the process as they are most commonly used off-label for MS according to the Atlas of MS (67% and 69% of respectively countries surveyed).

   Moreover, MSIF applied for MS treatments to be added to the World Health Organisation (WHO) Essential Medicine List (EML) in 2019 together with the World Federation of Neurology and all regional TRIMS networks. The application received a large number of public letters. The WHO Expert Committee did not recommend the addition of the medicines, but emphasized the need to consider all commonly used disease-modifying therapies (DMTs) for MS, specifically naming azathioprine and rituximab.

   In the future, other off-label DMTs could also be assessed by MSIF or other groups or organisations.

   The two DMTs were not reviewed because we think they are similar to each other or should be used under similar clinical circumstances:

   - Rituximab has been noted to be used in many high-income countries and it has the same mode of action, B-cell depletion, as other on-label anti-CD20 DMTs (e.g. ocrelizumab, ofatumumab). There are several ongoing clinical trials to assess rituximab use in MS. Rituximab is also listed by the MENACTRIMS and EAN/ECTRIMS treatment guidelines.

- Azathioprine use is more common in low income countries and there are no on-label DMTs for MS that have the same mode of action as azathioprine. There are no ongoing clinical trials with azathioprine in MS that we are aware of.

3. Is the MOLT panel putting forward azathioprine and rituximab to the World Health Organization (WHO) Essential Medicines List (EML)?

   The MOLT guidelines are a separate piece of work from MSIF's applications to add MS treatments on the WHO EML. However, the MOLT guidelines will be useful for future applications, as WHO feedback in 2019 requested azathioprine and rituximab should be considered for any revised application.

4. Why do the guidelines not cover Neuromyelitis Optica Spectrum Disorder (NMOSD) and MOG antibody associated disorders? NMOSD and MOG antibody associated disorders are more prevalent than MS in some areas of the world. Both azathioprine and rituximab are used off-label to treat NMOSD and MOG antibody associated disorders.

   NMOSD and MOG antibody associated disorders are outside the scope of these guidelines, which only focus on MS. We have noted that differential diagnosis between NMOSD / MOG antibody associated disorders and MS may be challenging in some settings. Azathioprine and rituximab have been reported to be used to treat all of these conditions.

5. Why do the guidelines not consider follow-on products (generics and biosimilars) with regulatory approval of on-label DMTs? Follow-on products can be much cheaper than originators and could be a good option in low-resource settings.

   There are many opportunities to improve access to treatment. Follow-on products with regulatory approval ensuring appropriate safety and efficacy data, are an important part of these efforts, as they can improve availability and reduce costs. There are several follow-on DMTs already on the market, e.g. glatiramer acetate and fingolimod. Rituximab and azathioprine also have follow-on products.

   These guidelines focused on off-label DMTs as these are already widely used, sometimes already available in health systems due to their registered indications for other diseases areas, but lack guidance on their use in clinical practice. Availability can make them a pragmatic option to consider where a range of on-label DMTs for MS are not available and affordable.

6. Why do the recommendations only compare azathioprine to interferon and not to other DMTs?

   The PICO question was set to compare azathioprine with 'other DMTs'. However, the systematic review only found evidence looking at azathioprine versus interferon. The panel did not feel comfortable making recommendations around other DMTs, as there were no data available.

From Evidence-to-Decision (EtD) PICO question (Population, Intervention, Comparator, Outcome) 6: "*A comprehensive systematic literature search including any other DMT as a potential comparison to azathioprine was performed. Other than interferon, only one trial (Kappos 1988) was retrieved, comparing azathioprine vs cyclosporine A. The Panel agreed that in current clinical practice cyclosporine A cannot be considered as a therapeutic option and decided not to consider such comparison.*"

7. Who is on the MOLT panel?

The MOLT panel is a multidisciplinary international guideline panel. The membership of the panel will remain anonymous until publication of the guideline, to protect the individuals involved from undue pressure from outside influence. There are 15 panel members, covering all WHO world regions. 53% of the panel were from low- and middle-income countries and there are two people affected by MS on the panel.

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

8. How can the certainty of evidence be 'very low' for both azathioprine and rituximab? There is much more evidence for the use of rituximab and it is routinely used in many high-income countries with strong health systems. Rituximab is often considered a high efficacy off-label DMT, how can it have the same certainty rating as azathioprine despite a greater magnitude of effect?

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 organizations, 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.

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. Randomized control trials are initially rated as high certainty and observational/non-randomized 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

randomized 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.

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.

For MOLT evidence, even though there was more evidence available (number of studies) for rituximab, this did not affect the certainty rating, as GRADE is not based on this parameter. Moreover, the different outcomes in rituximab evidence ranged from moderate to very low. For azathioprine, the certainty rating ranged from low to very low. However, as the overall rating is based on the lowest certainty of a critical outcome, all recommendations are based on very low certainty of evidence.

For MOLT, a limitation of the GRADE certainty assessment is that it does not allow for a more nuanced differentiation within a certainty category. GRADE allows a standardized approach for quality of evidence and the research team's assessment conclude both evidence for azathioprine and rituximab to be very low. However, the MOLT panel recognizes that the published evidence-base available for azathioprine and rituximab are different. Overall, there was more evidence for rituximab than for azathioprine, but this does not affect the certainty rating. Furthermore, some of the critical outcomes for the effects of rituximab were rated at higher certainty than for azathioprine.

We recognize that while Phase III randomised trial evidence is not available for either of these drugs, there are several investigator-led trials ongoing for rituximab. We note that large industry

led trials are not likely to be conducted for either drug, so judgments about their (already common) use need to be pragmatic.

If there are any errors that you have noted in the implementation of GRADE methodology to the MOLT certainty ratings, please let us know.

9. Did MOLT only consider randomised-controlled trials? A lot of the rituximab evidence comes from Swedish registry studies.

For the evidence review for MOLT, the research team considered all published controlled trials (randomised-controlled trials and non-randomised controlled studies). These include the Swedish registry studies for rituximab. The non-randomised controlled studies include: Granqvist 2018; Alping 2016; Alping 2020; Boremalm 2019; Evertsson 2020; Luna 2020; Spelman 2018; Naegelin 2019.

The Cochrane systematic review protocols can be found here:
Azathioprine: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015005/full
Rituximab: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013874/full

10. Have long-term safety data for azathioprine and rituximab been considered when making the recommendation?

The research team assessed all available evidence using inclusion/exclusion criteria as defined in the following protocols:

Azathioprine: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015005/full
Rituximab: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013874/full

The panel commented on a lack of good-quality long-term data, which was noted in the EtDs of the PICO questions.

11. Was COVID-19 considered when making the recommendations?

The Panel noted that additional data are emerging on the potential adverse effects of anti-CD20 therapies (e.g. rituximab, ocrelizumab) in patients with COVID-19 and possibly negative effect on vaccination efficacy. These data were not explicitly considered by the panel because the relevant publications appeared after the systematic review was complete. This note is however included in the undesirable health effects and justification of the recommendations.

For azathioprine, the studies of COVID-19 in people with MS have not been able to separate out the effect of azathioprine. However, data from other diseases areas may be useful for assessing impact of COVID-19 and vaccination for people with MS on azathioprine.

12. How can the certainty of effects of azathioprine and interferon be comparable? There are very little data for azathioprine, and interferon has been in use for over 20 years in routine clinical practice, and there is a large amount of evidence to support its use.

The MOLT panel assessed evidence for azathioprine versus no DMT and azathioprine versus other DMTs. For the other DMTs comparison, the research team only found evidence for azathioprine versus interferon, no evidence for other DMTs were found.

The direct evidence for health outcomes (head-to-head trials) of azathioprine versus interferon probably favoured azathioprine. However, the certainty of the evidence was very low and the effect of azathioprine in larger trials is unknown. To support the MOLT panel's decision-making in regards to azathioprine versus interferon, the research team also identified systematic reviews on interferons versus no DMT randomised controlled trials and non-randomised controlled studies, the analysis is included in the Evidence-to-Decision framework.

Interferon vs placebo evidence was also found to be of very low certainty, despite the higher number of patients. The certainty of evidence for outcomes assessed for azathioprine versus interferon ranged from low to very low. The certainty of evidence for outcomes for interferon versus no DMT, ranged from moderate to very low. However, as the overall rating is based on the lowest certainty of a critical outcome, both were found to be very low certainty of evidence. GRADE is based on assessment of domains, i.e. risk of bias, inconsistency, imprecision, indirectness and publication bias. The number of studies in the evidence review, i.e. more studies, does not necessarily mean higher certainty. For MOLT, a limitation of the GRADE evidence assessment is that it does not allow for a more detailed differentiation within a certainty category. GRADE uses a standardized approach for certainty of evidence and the research team's assessment conclude evidence to be very low certainty.

Panel members noted that as these trials are older, the diagnostic criteria used were not differentiating between NMOSD and MS. As azathioprine is also used to treat NMOSD, but interferon makes NMOSD patients worse, a mixed population in these trials may influence the health outcome difference between azathioprine and interferon to favour azathioprine. The Panel felt the amount and quality of evidence considering this direct comparison was low.

The panel noted that a recommendation on the use of interferon was outside of the scope of the guideline.

The MOLT recommendation:
The MOLT Panel suggests using azathioprine or interferon for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence).
Remark: Azathioprine use is conditional on the lack of interferon or other treatment options that are available and affordable.

The MOLT panel is not suggesting that access to interferon should be limited based on this recommendation. The recommendation for azathioprine is conditional on interferon and other DMTs not being available and affordable to the person with MS.

13. If the certainty rating is very low for both azathioprine and rituximab, does that mean they are similar DMTs with similar effectiveness?

No. Azathioprine and rituximab have different modes of action. Azathioprine inhibits purine synthesis, affecting white blood cells, causing immunosuppression. Rituximab is a chimeric monoclonal antibody targeted against CD20, which is a surface antigen present on B cells.

The GRADE methodology is very structured and the certainty of evidence for both was rated 'very low'. There are differences in the amount of data and magnitude of association, but the overall certainty rating is very low.

Rituximab has been noted to be used in many high-income countries, and there are other on-label anti-CD20 DMTs for MS (e.g. ocrelizumab, ofatumumab). There are several ongoing clinical trials to assess rituximab use in MS. Rituximab is also listed by the MENACTRIMS and EAN/ECTRIMS treatment guidelines as a DMT. The panel thought that rituximab would improve equity due to the relatively low cost, allowing people in low-resource settings to have access to treatment for MS with a monoclonal antibody.

Azathioprine use is more common in low income countries and there are no on-label DMTs for MS that have the same mode of action as azathioprine. There are no ongoing clinical trials with azathioprine in MS that we are aware of.

In the multi-therapy comparison, the panel concluded that rituximab is preferred over azathioprine, primarily for its desirable effects.

14. If the certainty of the evidence is very low, should there be a clinical trial to gather more data?

The MOLT panel identified the following research priorities:

Azathioprine – relapsing forms of MS:

Azathioprine vs no DMT
"The Panel did not consider there to be any research priorities as 'no disease-modifying therapy' would not be considered an ethical option for people with MS."

Azathioprine vs other DMTs
"The Panel recognised the very low level of certainty of the evidence for the direct comparison between azathioprine and interferon. Research to further consider this question may be considered unethical if other, more appropriate, disease-modifying therapies are available in a health system."

Rituximab – relapsing forms of MS:

Rituximab vs no DMT
"The Panel did not consider there to be any research priorities as 'no disease-modifying therapy' would not be considered an ethical option for people with multiple sclerosis."

Rituximab vs other DMTs
"The Panel identified the following research priorities:
- High quality head-to-head randomised controlled trials between rituximab and a range of comparators would improve certainty of evidence and inform how rituximab's efficacy and safety profile differs from other disease-modifying therapies.
- Studies evaluating long-term outcomes of rituximab and a range of comparators would improve certainty of evidence.
- Studies to evaluate the cost-effectiveness and cost of rituximab would better inform pharmaceutical policy and reimbursement decisions."

Rituximab – progressive forms of MS:

Rituximab vs no DMT
"The Panel identified the following research priorities:
- More and better-quality trials considering active progressive forms of multiple sclerosis would improve certainty of evidence.
- Studies evaluating long-term outcomes of rituximab would improve certainty of evidence.
- Studies to evaluate the cost-effectiveness and cost of rituximab would better inform pharmaceutical policy and reimbursement decisions."

Rituximab vs other DMTs
"The Panel identified the following research priorities:
- More and better-quality trials considering active progressive forms of multiple sclerosis would improve certainty of evidence.
- High quality head-to-head randomised controlled trials between rituximab and a range of comparators would improve certainty of evidence and inform how rituximab's efficacy and safety profile differs from other disease-modifying therapies.
- Studies evaluating long-term outcomes of rituximab and a range of comparators would improve certainty of evidence.
- Studies to evaluate the cost-effectiveness and cost of rituximab would better inform pharmaceutical policy and reimbursement decisions."

15. Why did you use GRADE? It does not seem sensitive enough to consider evidence for MS and off-label DMTs.

GRADE methodology is an internationally recognized, systematic way of assessing evidence. We used GRADE for the MOLT 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 that there is recognition and understanding of the certainty of evidence associated with off-label treatments. It is important to separate the judgment on **certainty of evidence** from judgments of **guideline recommendation**.

MOLT recommendations

16. Do the recommendations suggest whether azathioprine or rituximab should be used as first line treatment?

    The wording 'first choice' refers to treatment naïve patients and is not intended to suggest first line treatment. The recommendations suggest rituximab should be considered among other DMTs when a range of DMTs are not available and affordable. Azathioprine should only be considered when no other DMTs are available and affordable. Azathioprine is not appropriate for people switching from therapy due to treatment failure, whereas rituximab may be considered in this context.

    The recommendations do not suggest first-, second- or third- line differentiation, but leaves this for the joint decision-making between the clinician and the person with MS depending on the specific clinical and personal circumstances. In many countries all DMTs are available as first-line, and there are data emerging that suggests early treatment with high efficacy DMTs may be more beneficial than escalation therapy (https://jamanetwork.com/journals/jamaneurology/article-abstract/2783261).

17. Are you recommending azathioprine only if on-label alternatives are not available and affordable?

    Yes, azathioprine is only recommended when no other DMTs are available and affordable. This is in line with circumstances before on-label DMTs for MS were available. Unfortunately, this is still the case in some low-resource settings.

    It would be a mis-interpretation of these guidelines to restrict the use of other DMTs based on the MOLT recommendations for azathioprine. 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. It is clear that azathioprine alone is not an adequate treatment option to provide for MS, and should only be considered when no other alternatives exist.

18. How can azathioprine or interferon be recommended for relapsing forms of MS as first choice treatment? Interferon has regulatory approval from the US FDA and European Medicines Agency (EMA) and azathioprine is off-label.

The MOLT recommendation "*The MOLT Panel suggests using azathioprine or interferon for relapsing forms of multiple sclerosis as first choice treatment (conditional recommendation, very low certainty of the evidence). Remark: Azathioprine use is conditional on the lack of interferon or other treatment options that are available and affordable.*" was noted as very low certainty of evidence and is conditional on the lack of interferon or other treatment options.

This recommendation was judged applicable within the scope of the guideline, as in many settings interferon may not be available and affordable, limited due to several factors, e.g. route of administration, cold-chain storage, and cost. The systematic reviews and GRADE methodology does not consider regulatory approval, but independently assesses the evidence available.

The MOLT panel assessed evidence for azathioprine versus no DMT and azathioprine versus other DMTs. For the other DMTs comparison, the research team only found evidence for azathioprine versus interferon and, in one study (Kappos 1988), versus cyclosporine A. No evidence for other DMTs were found. However, the MOLT panel "*…agreed that in current clinical practice cyclosporine A cannot be considered as a therapeutic option and decided not to consider such comparison.*" (from Evidence-to-Decision (EtD) PICO question (Population, Intervention, Comparator, Outcome) 6.

The direct evidence for health outcomes (head-to-head trials) of azathioprine versus interferon probably favoured azathioprine. However, the certainty of the evidence was very low and the effect of azathioprine in larger trials is unknown. To support the MOLT panel's decision-making in regards to azathioprine versus interferon, the research team also identified systematic reviews on interferons versus no DMT randomised controlled trials and non-randomised controlled studies, the analysis is included in the Evidence-to-Decision framework.

Interferon vs placebo evidence was also found to be of very low certainty, despite higher number of patients. The certainty of evidence for outcomes assessed for azathioprine versus interferon ranged from low to very low. The certainty of evidence for outcomes for interferon versus no DMT, ranged from moderate to very low. However, as the overall rating is based on the lowest certainty of a critical outcome, both were found to be very low certainty of evidence. GRADE is based on assessment of domains, i.e. risk of bias, inconsistency, imprecision, indirectness and publication bias, but does not consider e.g. number of studies in the evidence review, as more studies do not necessarily mean better quality. For MOLT, a limitation of the GRADE evidence assessment is that it does not allow for a more detailed differentiation within a certainty category. GRADE allows a standardized approach for certainty of evidence and the research team's assessment conclude evidence to be very low certainty.

Panel members noted that as these trials are older, the diagnostic criteria used were not differentiating between NMOSD and MS. As azathioprine is also used to treat NMOSD, but interferon makes NMOSD patients worse, a mixed population in these trials may influence the health outcome difference between azathioprine and interferon to favour azathioprine. The Panel felt the amount and quality of evidence considering this direct comparison was low.

The panel noted that a recommendation on the use of interferon was outside of the scope of the guideline.

The MOLT panel is not suggesting that access to interferon should be limited based on this recommendation. The recommendation for azathioprine is conditional on interferon and other DMTs not being available and affordable to the person with MS.

19. Are you recommending rituximab only if on-label alternatives are not available and affordable?

No, the recommendations relating to rituximab are within the context where **a range of DMTs are not available and affordable**. Different clinical scenarios require different treatment approaches, and off-label use of DMTs to treat MS should be driven by the need to protect the person's health. In some circumstances, rituximab may be a more appropriate treatment approach than an on-label moderate efficacy DMT. Which treatment approach is most appropriate depends on the clinical and personal circumstances of the person affected and should be a joint decision between the treating clinician and person with MS.

20. Rituximab is widely used in some countries which are not considered low-resource settings, but the assessment shows the certainty of evidence is low. Should rituximab not be used in high income countries?

Rituximab is already widely used in some countries and areas e.g. in Sweden, British Columbia in Canada some parts of the US. The MENACTRIMS and EAN/ECTRIMS guidelines lists rituximab among the list of DMTs for MS.

The MOLT guidelines are focused on **low-resource settings where a range of on-label DMTs are not available and affordable**. The consideration of high income countries is outside the scope of the recommendations.

However, it is important to note that there are no financial incentives for industry to run clinical trials with rituximab. A number of pharmaceutical companies have other on-label CD20 therapies on the market (e.g. ocrelizumab, ofatumumab) which have a longer patent life and different price to rituximab. There are also several non-industry funded trials ongoing for rituximab.

21. Do you have a recommendation for the use of azathioprine and rituximab for pediatric MS? Rituximab is often used to treat pediatric MS.

The guideline is based on systematic reviews of the adult population and evidence for under 18 year old's was not included or assessed. Pediatric MS is therefore outside of the scope of the guideline. We would welcome an associated comment from experts on this topic.

22. What dosing do you recommend for azathioprine and rituximab? I hear that lower dose rituximab may improve safety outcomes.

The suggested dose of azathioprine and rituximab is not part of the recommendations.

Commonly reported dosage:

Azathioprine: Common target dose in clinical practice is 2-3mg/kg/day
Rituximab: Common starting (or induction) dose in clinical practice is 2 x 500 mg (or 1000 mg), two weeks apart, followed by a maintenance dose of 500 mg (or 1000 mg) every six to 12 months.

23. What happens if other DMTs become available after treatment with off-label DMTs has started?

During follow-up, if other DMTs become available for the person with MS, they should be discussed to consider desirable and undesirable effects and the benefits and harms of switching.

Implementation

24. Will promoting these recommendations risk health insurance and health systems to stop providing on-label DMTs as the off-label DMTs can be cheaper?

It would be a misinterpretation of these recommendations for health insurance and health systems to limit access to on-label DMTs. One of the general principles outlined in our recent publication *"Ethical use of off-label disease-modifying therapies for multiple sclerosis"* (https://journals.sagepub.com/doi/full/10.1177/13524585211030207) is that off-label use of DMTs to treat MS should be driven by the need to protect the person's health, not to save costs. Off-label use should be considered when on-label DMTs are not tolerated, unsuitable for the best clinical outcome, unavailable or unaffordable.

Azathioprine is recommended only when **no other DMTs are available and affordable**. This means that under such circumstances, the person with MS would have no other realistic treatment option.

Rituximab is recommended when **a range of DMTs are not available and affordable**. In these circumstances, the best clinical outcome may suggest using off-label rituximab rather than a e.g. a moderate efficacy on-label DMT. This is an important distinction as it would allow people in low-resource settings, to have access to treatment for MS with a monoclonal antibody. It is important that the details are explained and discussed with the person with MS, and that the treating clinicians and person with MS make a decision together on what the best course of action may be.

25. If azathioprine is recommended will that mean my health system may not provide high efficacy DMTs? Access to high efficacy DMTs is poor in low-resource settings, should we not focus on promoting access to high efficacy DMTs?

Azathioprine is recommended only when no other DMTs are available and affordable. This means that under such circumstances, the person with MS would have no other realistic treatment option. A range of DMTs should be available to treat different clinical scenarios, at different stages of the diseases course, and to ensure the ability to switch to different therapies in case of adverse events or lack of treatment response. 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.

We have noted a lack of access to high efficacy monoclonal DMTs, especially in low and middle-income countries (Figure 1C in https://journals.sagepub.com/doi/full/10.1177/13524585211030207). 100% of low income countries, and 50% of lower middle income countries, do not have access to on-label monoclonal therapies. In addition, there are emerging data suggesting that early treatment with high efficacy DMTs may be more beneficial than escalation therapy (https://jamanetwork.com/journals/jamaneurology/article-abstract/2783261), suggesting access to these DMTs should be improved.

Our work on MSIF Essential Medicines (MEM), that will create guidelines on essential medicines for low-resource settings and include an application to the WHO Essential Medicine List (EML), will address this question more systematically.

26. When you say 'available', what does it mean? Are azathioprine and rituximab available in in low-resource settings?

The concept of availability is very important for MOLT work. Off-label treatments by definition are used for other conditions and are therefore often already present and available for use in many health systems, and healthcare professionals may be familiar with their use. Both azathioprine and rituximab are listed on the WHO EML for other conditions.

To understand availability of DMTs on a country level, we have collected data for the Atlas of MS (https://www.atlasofms.org), and analysed 137 national essential medicines lists from the WHO database. The results are summarised in our recent publication (Figure 2 and Table 1 https://journals.sagepub.com/doi/full/10.1177/13524585211030207). It is important to note that availability of medicines is not binary (i.e. yes or no for a country) and can vary greatly within countries, different cities, hospitals, health systems or insurance providers, and timing of the year or budget cycle.

27. 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 azathioprine and rituximab, as well as, on-label DMTs. The analysis can be found in the EtDs.

Our recommendations are conditional on other DMTs not being available and affordable. This is in recognition that many instances, on-label 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 on-label DMTs and azathioprine or rituximab can make MS treatment possible.

Our stakeholders have raised concerns that health insurance providers may switch to 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.

28. Rituximab requires infusion suites. How feasible is administration in low- and middle-income countries?

The panel discussed access and availability of infusion suites, as noted in the following paragraphs from the EtDs:

"*The use of rituximab requires specialist care, including infusion facilities, and some additional laboratory tests, e.g. CD20/CD19 monitoring and pre-screens. These tests may not be available in all countries. These requirements are also valid for a number of other DMTs.* "

"*The Panel noted that rituximab is already used in a range of countries across different income levels. The low cost allows low-resource health providers and people who may have to pay a large proportion of the cost out-of-pocket to get access to monoclonal antibody therapy. The infrequent administration facilitates care for people who travel frequently or who may have to travel far to reach a hospital or health facility.*"

In conclusion, the panel felt this was an important point, but did not feel this was a significant barrier specifically for rituximab. Firstly, rituximab is already successfully used in many low- and middle-income countries, other similar DMTs would require infusion facilities too, and lastly the infrequency of infusions can make it more feasible than other DMTs.

Further resources:

1. Learning modules for World Health Organization (WHO) guideline developers and other guideline developers: https://www.youtube.com/watch?v=q1j-54Prn1k&list=PLGaL88PiuG8AE7Xlz9z99GKTxum4bLYAq&index=4
2. Interpreting GRADE's levels of certainty or quality of the evidence: GRADE for statisticians, considering review information size or less emphasis on imprecision? https://www.jclinepi.com/article/S0895-4356(16)30067-1/fulltext
3. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes https://www.jclinepi.com/article/S0895-4356(12)00025-X/fulltext