

Regione Emilia-Romagna CURA DELLA PERSONA, SALUTE E WELFARE





Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System



DEPARTMENT OF HEI Health Research Methodology

Collaboration and synergy among different actors making or influencing decisions on drug utilization may avoid duplication of efforts, resource waste and inconsistency

Improving Access to Essential Medicines Through a Synergic Approach. WHO Essential Medicines List Application of Treatments for Multiple **Sclerosis**.

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BACKGROUND

- Healthcare decision making often suffers from poor coordination among involved actors (systematic reviews authors, guideline developers, essential medicines decision makers, etc.). This may lead to duplication of efforts and decision misalignment [1]
- Updated every 2 years by an Expert Committee appointed by WHO, the **WHO Essential Medicines List (EML)** contains the medicines considered to be the most effective and safe to meet the priority health needs of a health system and is intended as a reference handbook for national and regional health authorities around the world.
- When developing an application for the inclusion of drugs in the WHO EML, equitable access to medicines at a global level is at stake, particularly in settings with limited resources
- Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system affecting about 2.8 million people worldwide, with a substantial health burden, being one of the most common causes of neurological disability in young people (onset age 20 – 50, female/male ratio 3:1).
- Variation in prevalence across global regions, largely linked to healthcare expenditure per capita, suggests MS may be largely underdiagnosed in lower income countries. No DMTs are currently included in the WHO EML We present a coordination effort among different entities aimed at submitting an application for the inclusion of diseasemodifying treatments (DMTs) for MS in the WHO EML.

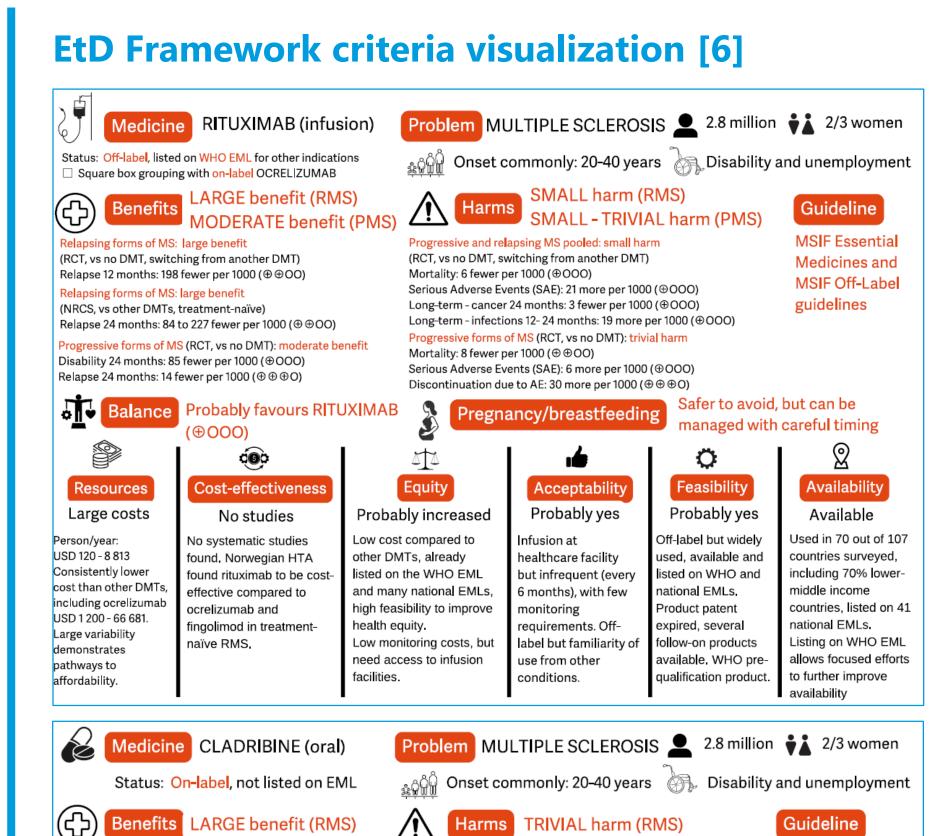
METHODS

- MSIF appointed the MS Cochrane Review Group to develop evidence syntheses on efficacy and safety of DMTs
- MSIF appointed two multi-stakeholder guideline development groups (MOLT, MSIF Off-Label Task Force, and MEMP, MSIF Essential Medicines Panel) to formulate evidence-based recommendations on the use of DMTs by means of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology
- Methodological support was provided by the McMaster University's GRADE Center, Department of Health Research Methods, Evidence & Impact (HEI)
- The criteria of the GRADE Evidence to Decision Framework were assessed from a limited resource setting perspective
- MSIF and the Bologna WHO Collaborating Centre co-developed an application, informed by the recommendations of the guideline development groups, for the inclusion in the WHO EML of DMTs.

RESULTS

- Systematic reviews and metanalyses on all available DMTs for MS [2-5]
- Development by the two multi-stakeholder guideline development groups (MOLT and MEMP) of evidence-based recommendations on off-label and labelled DMTs for MS
- Submission to the WHO EML Secretariat of an application for the inclusion of the first-ever DMTs for MS (rituximab, cladribine, glatiramer acetate) in the WHO Essential Medicines List [6]

CONCLUSIONS



Benefits LARGE benefit (RMS) Relapsing forms of MS (RCT, vs no DMT): Relapse 24 months: 240 fewer per 1000 ($\oplus \oplus \oplus \oplus$)

Favours CLADR BIN

Disability 24 months: 53 fewer per 1000 ($\oplus \oplus OO$)

QoL (EQ-5D VAS): SMD 0.19 SD higher ($\oplus \oplus \oplus O$)

QoL (EQ-5D index): SMD 0.24 SD higher (⊕ ⊕ ⊕ O)

Balance

Relapsing forms of MS (RCTs, vs no DMT): Mortality: 0 fewer per 1000 ($\oplus \oplus \oplus O$) Serious Adverse Events (SAE): 27 more per 1000 (⊕OOO) Discontinuation due to AE: 18 more per 1000 ($\oplus \oplus OO$)

regnancy/breastfeeding

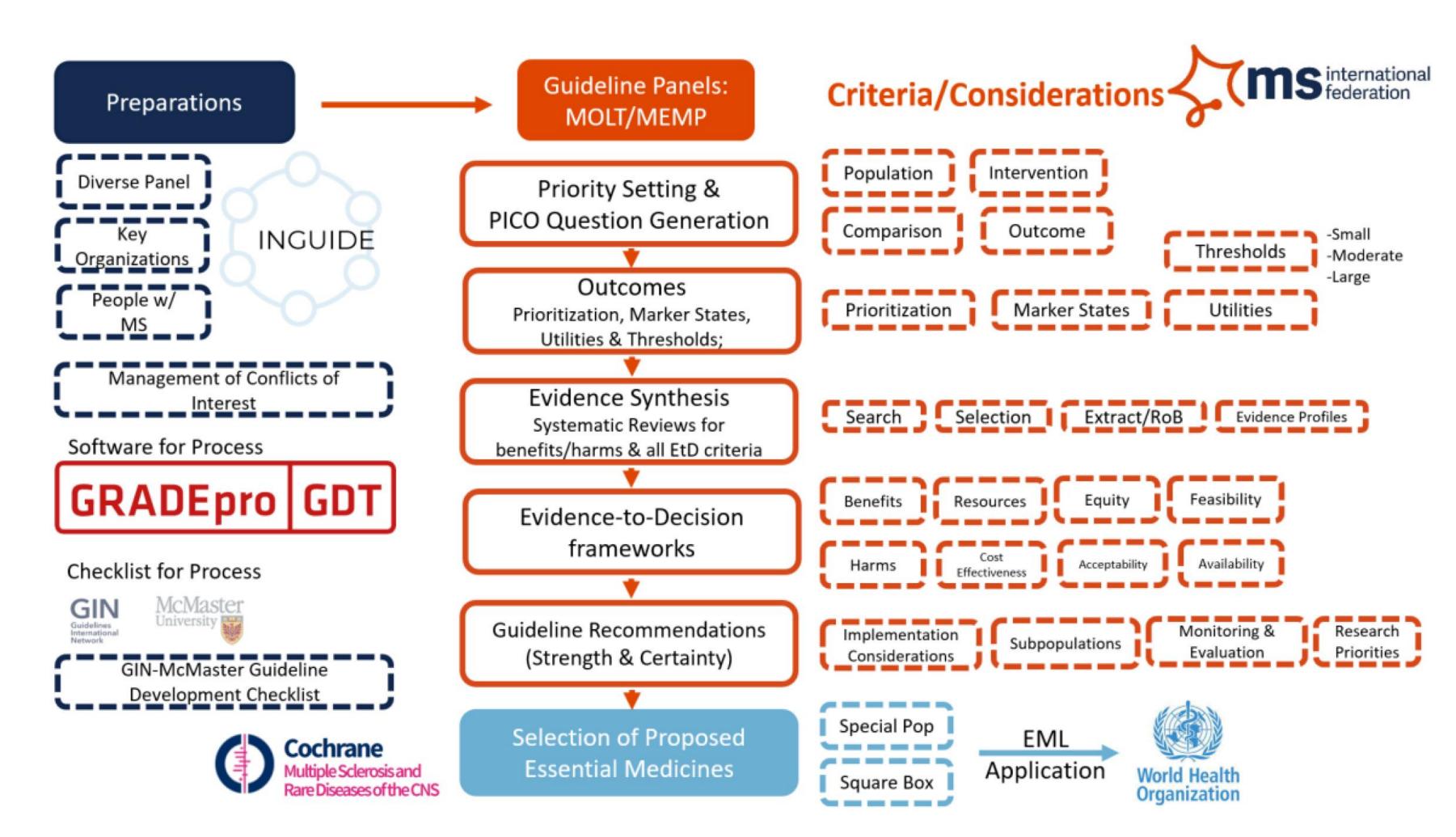
MSIF Essentia Medicines guidelines

Contraindicated

pregnancy can be planned

utside treatment period

- A synergic effort among organisations with different roles in the decisionmaking process led to evidence syntheses and evidence-based recommendations informing decisions by the WHO Expert Committee on the inclusion of medicines for MS in the EML
- Early planning alignment of guideline development groups mandated by a representative advocacy group facilitated shared participation of all key stakeholders and broad endorsement [7]
- Development of recommendations by means of the GRADE EtD Framework allowed shared assessment of criteria specific to the perspective of limited resource settings adopted by the WHO EML application developers [7]



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Resources	Cost-effectiveness	Equity	Acceptability	Feasibility	Availability
Large costs	Probably favours	Probably reduced	Yes	Probably yes	Probably no
Person/year: USD 6 602 - 62 628 2 years treatment only Large variability demonstrates pathwa to affordability throug voluntary licencing, pooled negotiation an	Cost-effective compared to ocrelizumab, alemtuzumab, natalizumab and ys fingolimod. h	Increased health equity but decreased financial equity. Low monitoring costs, oral mode of administration. Listing on WHO EML would reduce costs and	On-label, oral medication with few monitoring requirements. Short treatment period, although further treatment for some people may be	On-label, oral medication that can be used at home, with few monitoring requirements. No cold-chain required. Large costs, with secondary patents expiring 2024-25.	Used in 52 out of countries surveye more common in Approved recently 2017. Listing on WHO E allows focused ef to improve availab
procurement if listed o WHO EML.	5n	increase health equity.	necessary.	expiring 2024 20.	
Medicine	(injection)	Froblem	MULTIPLE SCLER	~	
Status: On-la	bel, not listed on EML	<u> </u>	. commonly: 20-40 ye		and unemploy
Benefits	LARGE benefit (RMS MODERATE benefit (ns TRIVIAL harm	n (RMS, PMS)	Guideline
Disability 24 months:		Relapsing forms of Mortality: 1 fewer p Serious Adverse Ev	[™] MS (RCTs, vs no DMT): per 1000 (⊕⊕OO) vents (SAE): 4 fewer per 100 ue to AE: 22 more per 1000 (MSIF Essenti Medicines guidelines
-	MS (RCT, vs no DMT): 68 fewer per 1000 (⊕OOO)	Mortality: 16 fewer Serious Adverse Ev	of MS (RCTs, vs no DMT): per 1000 (⊕⊕⊕O) vents (SAE): 9 more per 1000 ue to AE: 36 more per 1000 (, ,	
	Probably favours GLATI ACETATE (⊕OOO)	RAMER 🄰 Pregn	ancy/breastfeedi	ng Can be used d pregnancy and	uring d breastfeeding
Resources Large costs	Cost-effectiveness Varies	Equity Probably no impact	Acceptability Probably yes	Feasibility Probably yes	Availabili Varies
Person/year: USD 960 - 12 566 Large variability demonstrates pathways to affordability through voluntary licencing,	Cost-effective compared to fingolimod, interferon beta 1b, but not dimethyl fumarate, peg-interferon beta 1a or teriflunomide. Indeterminate compared to interferon beta 1a.	Increased health equity but decrease financial equity. Low monitoring costs, safe to use in pregnancy. Listing on WHO EML would reduce costs and	On-label with very few monitoring requirements. Frequent injections requiring cold-chain but which can be done at home.	On-label with very few monitoring requirements. Can be useed in	Used in 65 out countries surve and listed on 19 national EMLs, more common HICs. Listing on WHC

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Methods for the linkage between MOLT/MEMP recommendations and the application for the inclusion of DMTs in the WHO EML [6]

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