Quality assurance criteria of Multiple Sclerosis patient management in Hungary and Central-Easter European countries

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Doctoral School of Clinical Medicine, Clinical and Experimental Neurosciences Program

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Original publications directly related to the Ph.D. thesis

I. **Kokas Z**, Sandi D, Fricska-Nagy Z, Füvesi J, Biernacki T, Köves Á, Fazekas F, Birkás AJ, Katona G, Kovács K, Milanovich D, Dobos E, Kapás I, Jakab G, Csépány T, Bense E, Mátyás K, Rum G, Szolnoki Z, Deme I, Jobbágy Z, Kriston D, Gerócs Z, Diószeghy P, Bors L, Varga A, Kerényi L, Molnár G, Kristóf P, Nagy ZÁ, Sátori M, Imre P, Péntek S, Klivényi P, Kincses ZT, Vécsei L, Bencsik K. Do Hungarian multiple sclerosis care units fulfil international criteria? *PLoS One*. 2022 Mar 3;17(3):e0264328. doi: 10.1371/journal.pone.0264328.

Q1

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II. **Kokas Z**, Járdánházy A, Sandi D, Biernacki T, Fricska-Nagy Z, Füvesi J, Bartosik-Psujek H, Kes VB, Berger T, Berthele A, Drulovic J, Hemmer B, Horakova D, Ledinek AH, Havrdova EK, Magyari M, Rejdak K, Tiu C, Turcani P, Klivényi P, Kincses ZT, Vécsei L, Bencsik K. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants. *Mult Scler Relat Disord*. 2023 Jan;69:104406. doi: 10.1016/j.msard.2022.104406.

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Q2

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II. Nyári A, **Kokas Z**, Szamosi S, Fricska-Nagy Z, Füvesi J, Kincses ZT, Biernacki T, Vécsei L, Klivényi P, Bencsik K, Sandi D. The 7-year follow-up of the Hungarian BICAMS validation cohort implies that cognitive performance may improve in multiple sclerosis patients. Neurol Sci. 2024 Jul;45(7):3369-3378. doi: 10.1007/s10072-024-07347-5.

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Q1

IF: 5.6

VI. Biernacki T, Sandi D, Fricska-Nagy Z, Kincses ZT, Füvesi J, Laczkó R, **Kokas Z**, Klivényi P, Vécsei L, Bencsik K. Epidemiology of multiple sclerosis in Central Europe, update from Hungary. Brain Behav. 2020 May;10(5):e01598. doi: 10.1002/brb3.1598.

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I. Sandi D, **Kokas Z**, Kincses ZT, Füvesi J, Fricska-Nagy Z, Vörös E, Biernacki T, Vécsei L, Klivényi P, Bencsik K. NEDA-state, psychological symptoms and quality of life are stable in natalizumab-treated multiple sclerosis patients: an up to 6-years long follow-up study. Heliyon

Abbreviations

ALM = alemtuzumab

ARR = annualized relapse rate

ASN = Austrian Society of Neurology

Au = Austria

CDMS = clinically definite multiple sclerosis

CIS = clinically isolated syndrome

CLA = cladribine

CNS = central nervous system

Cr = Croatia

CSF = cerebrospinal fluid

Cz = Czecz Republic

DIS = dissemination in space

DIT = dissemination in time

DMF = dimethyl fumarate

DMSG = German Multiple Sclerosis Society

DMT = disease modifying therapy

DSNS = Danube Symposium for Neurological Sciences

EAN = European Academy of Neurology

ECTRIMS = European Committee for Treatment and Research in Multiple Sclerosis

EDSS = Expanded Disability Status Scale

FG = fingolimod

GA = glatiramer acetate

Gd+ = gadolinium

GMSR = German Multiple Sclerosis Registry

GP = general practitioner

HCP = healthcare provider

HEDMT = highly effective disease modifying therapy

Hu = Hungary

ICD-10 = International Classification of Diseases 10th edition

IFN-β = interferon beta

MDT = multidisciplinary team

MoHI = Ministry of Health Institute

MRI = magnetic resonance imaging

MS = multiple sclerosis

MSCU = multiple sclerosis care unit

NAT = natalizumab

NEDA-4 = no evidence of disease activity-4

NfL = neurofilament light chain

NHIF = National Health Insurance Fund

N/A = no data available

OCB = oligoclonal band

OCR = ocrelizumab

OCT = optical coherence tomography

Pl = Poland

PML = progressive multifocal leukoencephalopathy

PolNS = Polish Neuroscience Society

PPMS = primary progressive multiple sclerosis

pwMS = people with multiple sclerosis

ReMus = Czecz Registry of Patients with Multiple Sclerosis

RIS = radiologically isolated syndrome

Ro = Romania

RPMS = relapsing progressive multiple sclerosis

RRMS = relapsing-remitting multiple sclerosis

Sk = Slovakia

Slo =Slovenia

SPMS = secondary progressive multiple sclerosis

Srb = Serbia

TFL = teriflunomide

USA = United States of America

VEP = visually evoked potential

WHO = World Health Organisation

Summary

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune demyelinating, neurodegenerative disease of the central nervous system. Because of the nature of the disease, for centuries the diagnosis of MS implied slowly accumulating disability, resulting in wheelchair confinement, bedridden state and death. However, almost 30 years ago, interferon-β, the first disease modifying therapy (DMT) was introduced, successfully changing the natural course of the disease. Nowadays over 15 DMTs are available, and with this therapeutic arsenal all courses of the disease can be treated, thus, physical- and cognitive abilities, and quality of life of patients can be preserved. Simultaneously over the years, disease course classification, imaging and diagnostic guidelines also frequently evolved. Currently, general practitioners and general neurologists cannot keep up with these changes to ensure patient equality. Keeping patient equality and complexity of MS in mind, with the introduction of the first DMT, initial MS centres in Hungary and in some other countries have been created, while other nations followed different strategies. However, with expanding information on MS, there was a growing need for the standardization of MS care. In 2018, the international therapeutic guideline disclosed that DMTs should only be administered in specialized MS centres. Then, in 2019 the MS care unit criteria, describing the personnel and instrumental conditions of a multidisciplinary MS centre was published.

Aims

In our evaluations we aimed to assess whether MS centres in Hungary and in Central Eastern European countries fulfil the international MS care unit recommendation, to gain information on DMT and registry use and patient population receiving care in centres.

Patients and methods

Both studies were conducted in the Department of Neurology, University of Szeged, Albert Szent-Györgyi Health Centre, Szeged, Hungary. We surveyed real-life operation of MS centres using a self-report questionnaire inquiring about MS care unit criteria, DMT and registry use, and patient number. Further research was also conducted to gain a comprehensive overview on the countries' health care background. We first performed a pilot investigation in Hungary, that was later expanded to nine Central-Eastern European countries partaking in the Danube Symposium for Neurological Sciences. Data were analysed using descriptive statistics.

Results

In the Hungarian MS care unit survey, we found that of the participating 29 centres, only 10 fulfilled minimum criteria of which 7 satisfied recommended conditions. Least prevalent specialists were spasticity and pain specialist, and neuro-ophthalmologist and oto-neurologist.

Regarding DMT use, all centres ensured low/moderately effective treatments, but only 15 centres provided the whole therapeutic arsenal. Concerning patient number, 27 respondent centres were responsible for the care of 7 213 individuals, which is below patient number based on prevalence estimates. In the international MS care unit survey 101 centres participated from 9 countries. In Austria and the Czech Republic patient management was pursued in a well-developed referral centres system, undergoing regular quality control. In 4/9 countries over 75% of institutes satisfied at least 75% of the MS care unit criteria, while in the rest of the countries, conditions displayed heterogenous fulfilment. Administrator, speech therapist, pain, continence, and spasticity specialist, oto-neurologist, and neuro-ophthalmologist were the most common shortcomings. Despite DMTs being reimbursed in all countries, the whole therapeutic arsenal was only ensured in all centres across 6 nations. In the rest of the countries the availability of highly effective DMTs was heterogenous. A national registry was available in 4 countries, accordingly, reported patient number corresponded with prevalence estimates, while in the rest of the nations, large gaps were discovered.

Discussion and conclusions

Our surveys yielded novel information on the real-world operation of MS centres. In Hungary spasticity and pain specialist, and neuro-ophthalmologist and oto-neurologist were common insufficiencies, which specialties play an important role in the management of people with progressive MS. Only half of the centres ensured every DMT, which can also be attributed to missing personnel and instrumental background. Reported patient number fell short of calculated patient number based on prevalence estimates, which can be explained by the fact that timely diagnosis and management of progressive MS is not resolved. In Central-Eastern European countries, due to distinct economic and health care backgrounds, and disparities due to variable institutional circumstances, differences were discovered on an international and national level. Administrators, speech therapists, pain, continence, and spasticity specialists, oto-neurologists, and neuro-ophthalmologists were the most common shortcomings. As DMTs were reimbursed among participating countries, their availability was dependent on institutional and national circumstances. Similarly to the Austrian and Czech centre system, with a close collaboration between centres, consulting hours even with the rarest specialties and appropriate inpatient background could be ensured, resulting in equality in access to care. With close cooperation between MS specialist, National Health Insurance Funds, and Ministry of Health Institutes and regular quality control, the quality of MS care might be even further improved.

I. Introduction

I.1. Brief epidemiology of MS

Multiple Sclerosis (MS) is an autoimmune, inflammatory, demyelinating, neurodegenerative disorder of the central nervous system (CNS), which - after traumatic injuries - is the second most common cause of physical disability among young adults (Vukusic S et al., 2001, Compston A et al., 2004). In young adulthood MS is the second most common neurological disorder after epilepsy, however, regarding the general population it is considered a rare disease. According to the World Health Organisation (WHO) data, MS affects approximately 2.8 million people worldwide, and almost 700 000 persons in Europe (Walton C et al., 2020, Iljicsov A et al., 2019). In Hungary the prevalence of MS is 101.8/100 000, thus thereabouts 10 000 people are affected by it (Biernacki T et al., 2020).

I.2. Symptoms of MS

MS is often referred to as a "disease with a thousand faces," highlighting the wide range of symptoms associated with it. Most common symptoms include visual and balance disturbances (optic neuritis, diplopia, nystagmus, vertigo, ataxia), motor and sensory impairment (paresis, intention tremor, hypaesthesia, paraesthesia), difficulty of speech and swallowing (dysarthria, dysphagia), bladder, bowel and sexual disfunction (urinary retention and incontinence, faecal incontinence, diarrhoea, obstipation, erectile dysfunction), changes in muscle tone and pain (spasticity, trigeminal neuralgia, chronic pain) (Tafti D, Ehsan M and Xixis KL, 2024). Physical status is commonly characterized by expanded disability status scale (EDSS) (Kurtzke JF, 1983). Aside from its well-known chronical physical disability-causing nature, MS also has a negative effect on cognition, and can potentially cause psychopathological symptoms, such as depression, anxiety and fatigue (Chiaravalloti ND and DeLuca J, 2008). Through these symptoms MS influences the choice of career, level of education, family planning, financial and existential aspects of life (Pfleger CC, Flachs EM and Koch-Henriksen 2010). Compared to the general population people living with MS have an increased likelihood of divorce, impairment of societal relationships and unemployment (Pfleger CC, Flachs EM and Koch-Hendriksen N, 2010). Furthermore, in comparison with other disorders, the MS-related mortality is higher than in cardio- and cerebrovascular diseases and early diagnosed breast cancer (Petty GW et al., 2005, Hooning MJ et al., 2006).

I.3. Natural disease course of MS

The natural course of MS displays a wide heterogeneity, portraying a vastly different effect on one’s physical and cognitive abilities, mental health, and quality of life (Confavreux C and Vukusic S, 2006). The majority of people experience their first symptoms in the age of 20 to 40

years, but approximately 5-10% of patients might have an early or late disease onset (Krupp LB et al., 2013, Bermel RA, Rae-Grant AD and Fox RJ, 2010). On one hand, 10-15% of patients experience slow worsening of symptoms from the beginning, called primary progressive MS (PPMS). Within this group, a rare entity is the relapsing progressive course (RPMS), that is described by slow worsening of symptoms with occasional relapses. Without treatment this population becomes severely disabled within 5 years, and bedridden after 10-12 years (Confavreux C and Vukusic S, 2006, Ontaneda D et al., 2017). On the other hand, approximately 90% of patients, during the first decade of the disease, experience acute or subacute attacks of new neurological symptoms or worsening of pre-existing ones, called relapse. By definition, these neurological symptoms occur without the presence of an infection, last for at least 24 hours, and there is at least a 30-day window between exacerbations. Without intervention in the first few years of the disease, these exacerbations reside spontaneously within 10 to 12 weeks and patients go into complete remission. However, later on, relapses heal with residual neurological symptoms, that accumulate over time, causing irreversible disability (Confavreux C and Vukusic S, 2006). After 15 to 25 years, relapses get less frequent and eventually disappear, while a period of steady worsening of neurological signs begin, called secondary progressive MS (SPMS).

I.4. Disease course classification of MS, disease activity

The first disease course classification was described by Lublin (Lublin FD and Reingold SC, 1996). According to the first classification, MS was divided into 5 subtypes: benign, relapsing-remitting, secondary progressive, primary progressive and relapsing-progressive MS. The term "benign MS" was later eliminated because individuals who initially experienced rare exacerbations (1 relapse every 2-3 years) after reaching an EDSS score of 3, progressed to an EDSS score of 6 at the same rate as those who had more frequent exacerbations early on (Ebers GC, 2001). This meant that even patients earlier classified into the “benign MS” category developed secondary progression later on, thus there was a growing need for a new disease course classification (Lublin FD et al., 2014, Ntranos A and Lublin F, 2016) (Figure 1).

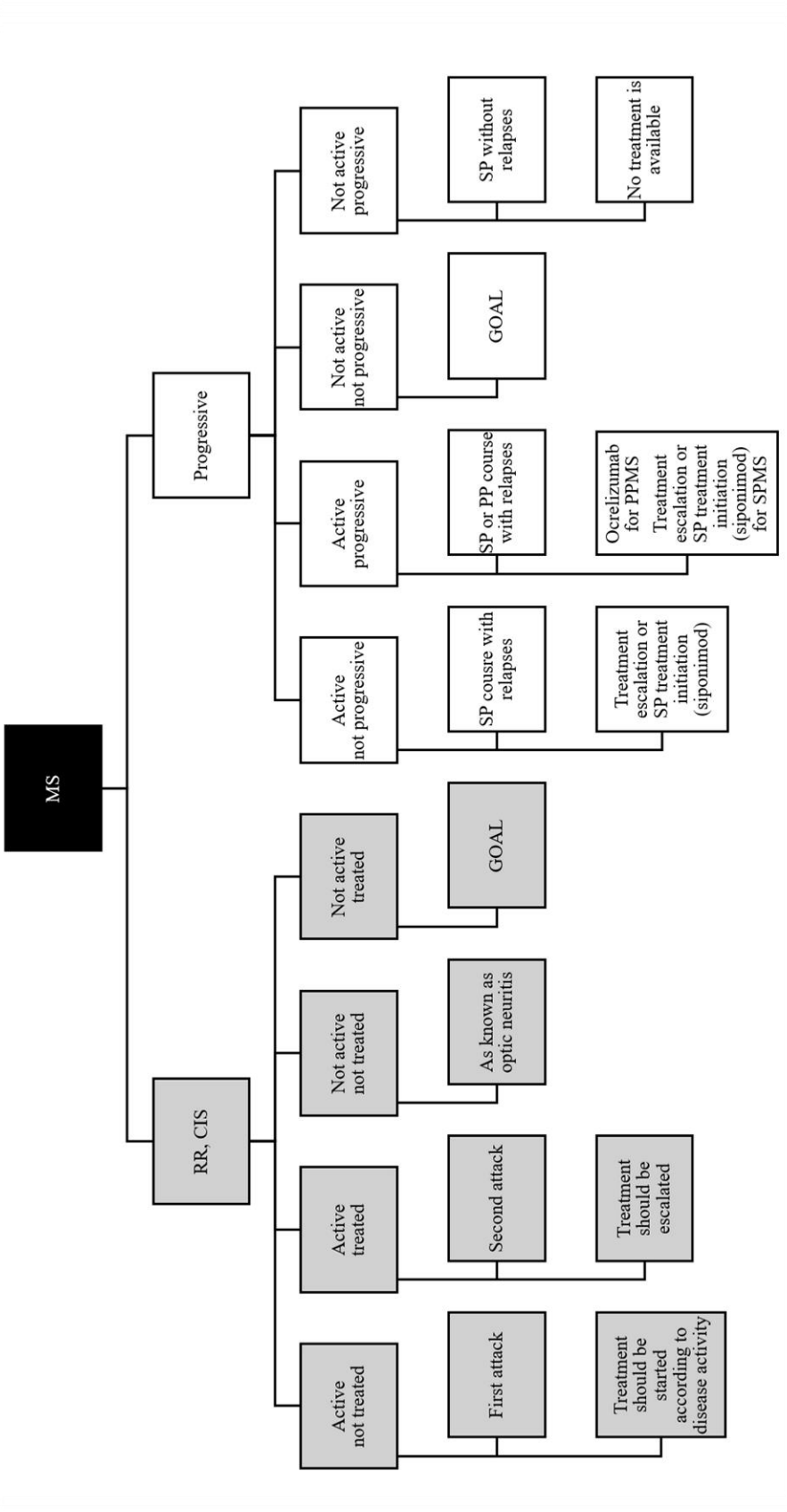

Figure 1: Latest disease course classification

Abbreviations: CIS = clinically isolated syndrome, MS = multiple sclerosis, PP = primary progressive, RR = relapsing remitting, SP = secondary progressive

According to the latest terminology MS can be categorised into relapsing-remitting and progressive course. The "preclinical state" of MS is labelled radiologically isolated syndrome (RIS) – when only accidental paraclinical findings (e.g. demyelinating lesions on magnetic resonance imaging (MRI)) foreshadow later disease activity. RIS does not belong to either the relapsing remitting or progressive MS category, as people with RIS may not develop any clinical signs later on (Lebrun-Frenay C et al., 2023). The first clinical event, called clinically isolated syndrome (CIS), belongs to the relapsing remitting spectrum. The progressive phenotype includes the primary progressive, secondary progressive and relapsing progressive subtypes. This classification also took into consideration disease activity (active, not active), therapeutic status (treated, not treated), and progression (progressive, not progressive). A disease is considered active, if new clinical attacks, EDSS progression, new or contrast enhancing MRI lesions or brain-volume-loss are present, and inactive if the no evidence of disease activity (NEDA-4) is fulfilled (Kappos L et al., 2016). According to these modifications in the relapsing remitting main category, four subcategories can be distinguished: active – not treated, active – treated, not active – treated, not active – not treated. In the progressive category, also four subcategories can be distinguished: active – not progressive, active – progressive, not active – not progressive, not active – progressive.

I.5. Diagnosis of MS

In the past, diagnosis of MS was purely clinical. If a person presented with multifocal neurological signs in different timepoints, and no other cause explanatory of these symptoms could be identified, a suspected or probable MS diagnosis was established. However, only autopsy reports could confirm a definite MS diagnosis (Schumacher GA et al., 1965). With the development of imaging technologies, MRI was included in the diagnostic criteria (Poser CM et al., 1983). According to the Poser criteria without using any paraclinical tests clinically definite, probable or possible diagnosis of MS could be made. With the inclusion of paraclinical tests, clinically definite MS (CDMS) with confirmative paraclinical findings and probable MS according to paraclinical findings could be distinguished. Still, the Poser criteria did not involve the diagnosis of PPMS. Nowadays, the cornerstones of MS diagnosis are MRI, cerebrospinal fluid (CSF) analysis and evoked potential tests, but it still remails a clinical diagnosis. It is based on confirmation of dissemination in time (DIT) and space (DIS). With rapidly evolving disease modifying therapies (DMT) and a narrow effective treatment window, quick diagnosis and ascertainment of disease activity became top priority. For that purpose, McDonald criteria were established in 2001, and modified in 2005, 2010 and 2017 (McDonald WI et al., 2001, Polman CH et al., 2005, Polman CH et al., 2011, Thompson AJ et al., 2018) (Table 1).

	2001 McDonald criteria	2005 McDonald criteria	2010 McDonald criteria	2017 McDonald criteria
CDSM (RRMS)	2 ONS, 2 relapses → no further tests needed 1 ONS 2 relapses → Proof of DIS is required: - with MRI - wait for 2nd relapse 2 ONS, 1 relapse → Proof of DIT is required: - with MRI - with MRI (≥2 MS specific lesions) and positive CSF - wait for 2nd relapse 1 ONS, 1 relapse → 1) Proof of DIS is required: - with MRI - with MRI (≥2 MS specific lesions) and positive CSF 2) Proof of DIT is required: - with MRI only - wait for 2nd relapse	2 ONS, 2 relapses → no further tests needed 1 ONS 2 relapses → Proof of DIS is required: - with MRI - wait for 2nd relapse 2 ONS, 1 relapse → Proof of DIT is required: - with MRI - with MRI (≥2 MS specific lesions) and positive CSF - wait for 2nd relapse 1 ONS, 1 relapse → 1) Proof of DIS is required: - with MRI - with MRI (≥2 MS specific lesions) and positive CSF 2) Proof of DIT is required: - with MRI only - wait for 2nd relapse	2 ONS, 2 relapses → no further tests needed 1 ONS 2 relapses → Proof of DIS is required: - with MRI - wait for 2nd relapse 2 ONS, 1 relapse → Proof of DIT is required: - with MRI - wait for 2nd relapse 1 ONS, 1 relapse → 1) Proof of DIS is required: - with MRI - wait for 2nd relapse 2) Proof of DIT is required: - with MRI - wait for 2nd relapse	2 ONS, 2 relapses → no further tests needed ***1 ONS 2 relapses with anamnestic proof of a relapse involving a different ONS → no further tests needed*** 1 ONS 2 relapses without anamnestic proof of relapse → Poof of DIS is required: - with MRI 2 ONS, 1 relapse → Proof of DIT is required: - with MRI - wait for 2nd relapse 1 ONS, 1 relapse → 1) Proof of DIS is required: - with MRI - wait for 2nd relapse 2) Proof of DIT is required: - with MRI - positive CSF - wait for 2nd relapse
CDSM (PPMS)	Positive CSF + proof of DIS: - ≥9 cerebral T2 lesions - ≥2 spinal cord lesions - 4-8 cerebral and 1 spinal cord lesions - 4-8 cerebral lesions and abnormal VEP - <4 cerebral and 1 spinal cord lesions and abnormal VEP + proof of DIT: - with MRI - at least one-year confirmed progression	***At least one-year confirmed progression, and 2 of the following:*** ***- ≥9 cerebral T2 lesions or ≥4 cerebral lesions and abnormal VEP*** ***- ≥2 focal spinal cord lesions*** ***- positive CSF***	At least one-year confirmed progression, and 2 of the following: ***- ≥1 lesion in at least 2 MS-specific*** locations - ≥2 focal spinal cord lesions - positive CSF	At least one-year confirmed progression, and 2 of the following: - ≥1 lesion in at least 2 MS-specific locations - ≥2 focal spinal cord lesions - positive CSF

DIS	DIS can be confirmed if 3 of the following criteria are present: - ≥9 T2 lesions or 1 Gd+ lesion - ≥3 periventricular T2 lesions - ≥1 juxtacortical lesion - ≥1 infratentorial lesion (1 spinal cord lesion may substitute a cerebral lesion)	DIS can be confirmed if 3 of the following criteria are present: - ≥9 T2 lesions or 1 Gd+ lesion - ≥3 periventricular T2 lesions - ≥1 juxtacortical lesion - ≥1 infratentorial lesion (1 spinal cord lesion may substitute a cerebral lesion)	***DIS can be established if ≥1 T2 lesions in ≥2 MS specific anatomical locations are present:*** ***- periventricular*** ***- juxtacortical*** ***- infratentorial*** ***- spinal cord***	DIS can be established if ≥1 T2 lesions in ≥2 MS specific anatomical locations are present: - periventricular - juxtacortical - infratentorial - spinal cord
DIT	DIT can be confirmed if: - a Gd+ lesion is present 3 month after the first relapse, and it is not related to the first symptoms - or a new T2 lesion is present 3 months after the occurrence of first symptoms and baseline MRI	DIT can be confirmed if: - a Gd+ lesion is present 3 month after the first relapse, and it is not related to the first symptoms - or a new T2 lesion is present 30 day after the occurrence of first symptoms and baseline MRI	***DIT can be confirmed if:*** ***- a new T2 or Gd+ lesion is present compared to baseline MRI regardless of the time passed*** ***- or simultaneous presence of T2 and Gd+ lesion at any timepoint***	DIT can be confirmed if: - a new T2 or Gd+ lesion is present compared to baseline MRI regardless of the time passed - or simultaneous presence of T2 and Gd+ lesion at any timepoint ***- or positive CSF***

Table 1: Evolution of the McDonald criteria

Abbreviations: CDMS = clinically definite multiple sclerosis, CSF = cerebrospinal fluid, DIS = dissemination in space, DIT = dissemination in time, Gd+ = gadolinium enhancing lesion, MRI = magnetic resonance imaging, MS = multiple sclerosis, ONS = objectifiable neurological sign, PPMS = primary progressive multiple sclerosis, RRMS = relapsing remitting multiple sclerosis, VEP = visually evoked potential

Segments highlighted by bold and italic style indicate the novelty of the actual guideline.

The diagnostic criteria of PPMS were first described in the 2005 modifications. The latest diagnostic criteria enable the quickest shift from CIS to CDMS, while preserving high specificity and sensitivity. In case of only one clinical attack, CDMS diagnosis can be made if 1) on the MRI two anatomical regions predilective of MS are present, as it proves DIS and 2) on the MRI, lesions show gadolinium enhancement (Gd+) or oligoclonal bands (OCB) are present in the CSF, because these results prove DIT (Figure 2, 3).

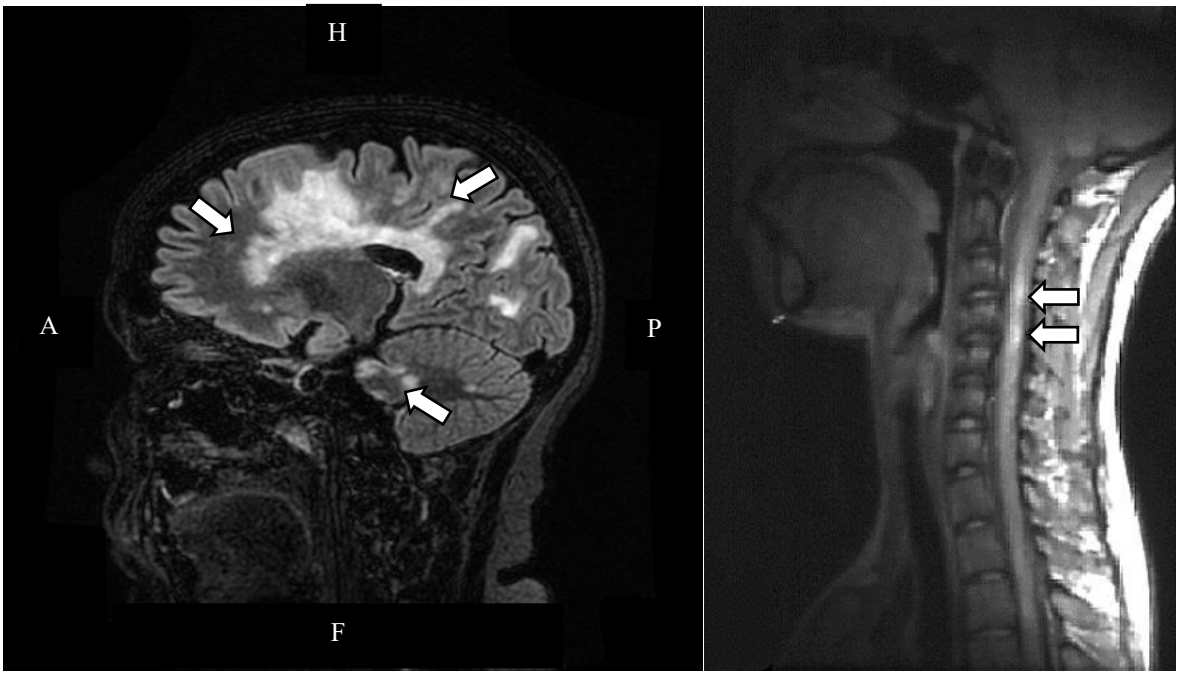

Figure 2: Brain (on the left) and spinal cord (on the right) MRI with multiple T2 lesions characteristic of MS indicated by white arrows

Abbreviations: A = anterior, F =feet, H =head MRI = magnetic resonance imaging, MS = multiple sclerosis, P = posterior

Source: Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of Szeged

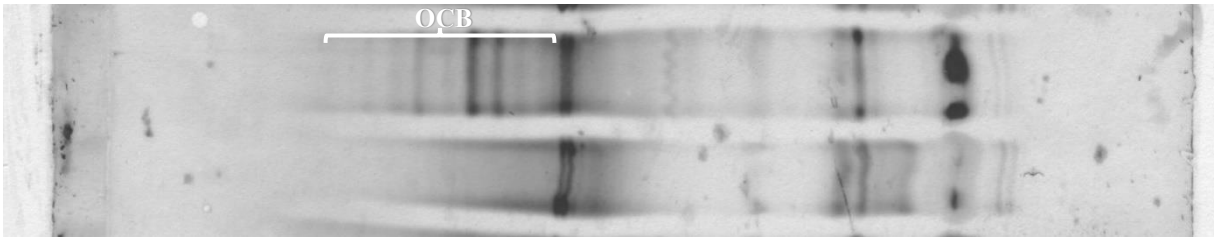

Figure 3: Isoelectric focusing of the cerebrospinal fluid (above) compared to the serum (below)

Abbreviations: OCB = oligoclonal bands

Source: Cerebrospinal Fluid Laboratory, Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of Szeged

After the diagnosis is made, disease activity can be determined by the overall and Gd+ lesion burden. Disease activity is based on baseline MRI lesion count. Moderate disease activity can be established if ≤6 T2 and no Gd+ enhancing lesions are present. In case of high disease activity ≥9 T2 lesion and at least 1 Gd+ enhancing lesion can be observed. If T2 lesion count exceeds 20 and more than 1 Gd+ enhancing lesions are present at once, aggressive disease course can be ascertained (Comi G et al., 2017). After the characterisation of disease activity, MS-specific treatment can be initiated accordingly.

I.6. Treatment of MS

There are three types of MS treatment: acute relapse treatment, symptomatic treatment, and DMTs. Since 1992 acute relapse treatment usually consists of parenteral megadose methylprednisolone therapy for 3-5 days, followed by a 10 day-long oral steroid course. In case of a severe or steroid-resistant neurologic symptoms, further plasma exchange might be considered. However, steroid treatment only results in a shortened remission time, it does not influence the natural course of the disease (Beck RW et al., 1992, Burton JM et al., 2012). Symptomatic treatment mainly focuses on relieving spasticity, vegetative disorders, pain, fatigue and treating depression and anxiety (Kesselring J and Beer S, 2005). On the other hand, DMTs with different mechanism of action, reduce the underlying inflammation and prevent demyelination. With timely and adequate intervention, DMTs can delay the onset of disability, might even prevent the development of residual neurological symptoms, thus, it can improve life expectancy (Hauser SL and Cree BAC, 2020, Grytten Torkildsen N et al., 2008). Therefore, even though to this day there is no cure for MS, the diagnosis of MS no longer equals prognosis. In the past three decades, the number of DMTs have expanded significantly. The first DMT, interferon-β (IFN-β) was introduced to the public in 1993 (Knobler RL et al., 1993). Nowadays over 15 DMTs are available, with several options both in the low/moderate and highly effective spectrum, enabling personalized treatment focusing on disease activity. With the current therapeutic arsenal, all courses of MS can be treated. Naturally with wider range of treatment choices comes a broader spectrum of side effects as well. Thus, treatment administration, DMT effectivity and side effects should be regularly monitored, and adverse reactions should be treated and reported immediately. Nevertheless, taking into consideration these possibilities, the known benefits of treatment use, far exceed the posed risks. With the current treatment options, in case of reoccurring disease activity, undesirable side effects, pregnancy, comorbidities or the occurrence of other influential factors, a therapeutic change is possible. Thus, early diagnosis and adequate treatment according to the latest diagnostic and therapeutic guidelines are of utmost importance (Montalban X et al., 2018a, Montalban X et al., 2018b).

1.7. Multiple sclerosis care

Historically, persons with chronic diseases were cared for similarly. Because of the lack of modern diagnostic tools and treatments, progressive neurological diseases faced comparable outcomes, thus were often treated as one condition. People usually received nursing, herbal medicine and ancient medical interventions, such as bloodletting and purging to relieve the body from “toxins” in order to regain balance and health. Later on, chronic neurological conditions were considered “nervous disorders”, thus lifestyle changes, stress relieving

techniques, balneotherapy and physiotherapy were recommended (Murray TJ, 2022). MS was first distinguished from other neurological disorders in 1868 by Jean-Martin Charcot (Charcot JM, 1868). As a result of his commitment, diagnosis of MS became possible worldwide. In 1884 the foundation of today's treatment regime was laid down by Pierre Marie, who hypothesized that MS was caused by an infection and recommended medications to reduce inflammation (Marie P, 1884). However, for several more decades, there was no substantial progress achieved regarding the treatment and care of people with MS (pwMS) (McAlpine D, 1955). Even in the past century, many neurologists after establishing the diagnosis, considering the lack of treatment, did not follow their patients. In this era, people after slowly losing the capability to care for themselves, usually received care at home from loved ones. Even though some hospitals and nursing facilities offered care for people in need, there were no designated centres. The subsequent advancement started with the end of World War II, as some rehabilitation centres undertook the responsibility to care not only for the wounded but also people living with chronic disability (Murray TJ, 2022). Later on, early MS clinics were established, focusing on general care and research. The greatest step toward today's MS care system initiated in 1993 with the introduction of the first DMT (Beck RW et al., 1992). In the European Union IFN-β was licensed in 1995 and was prescribed by local neurologists. After prescribing the DMT, usually general practitioners (GP) or in some regions general neurologists provided MS care. In some countries, also in Hungary, because of the high retail price of the DMT, neurologists and National Health Insurance Funds (NHIF) funded specialized MS centres to ensure adequate treatment use. Understandably though, because of different financial, economic and health care systems internationally, MS care could not be standardized. Since then, as more research proved the complexity of MS, there have been endeavours to shift MS care toward a centralized, multidisciplinary approach. As diagnostics, differential diagnostics, determination of disease course and ensuring the entire therapeutic arsenal are cost- and human-resource-demanding, it became clear that sophisticated patient management requires both technically and professionally highly equipped MS centres. In 2018 the European Committee for Treatment and Research in Multiple Sclerosis and European Academy of Neurology (ECTRIMS/EAN) therapeutic guideline suggested that DMTs should only be administered in MS care units (Montalban X et al., 2018a, Montalban X et al., 2018b). Then in 2019, the first international recommendation describing the criteria of a multidisciplinary MS care unit (MSCU) was published, proposing the adaptation of these criteria (Soelberg Sorensen P et al., 2018). Firstly, Latin America took upon the adaptation, however, there was no real-world data regarding the operation of already existing MS centres (Cristiano E et al., 2021).

II. Objectives

Our main goals were to:

1) Assess whether MS centres in Hungary and in Central-Eastern European countries partaking in the Danube Symposium for Neurological Sciences (DSNS), fulfil international recommendation on MS care.
2) Gather information on ongoing MS care systems in Hungary and internationally to gain a comprehensive overview on current MS care.
3) Assess DMT use in Hungary and internationally, to evaluate equality regarding DMT use is ensured.
4) Collect data on actual patient number receiving care in Hungary and internationally, to compare to estimated patient number according to national prevalence studies, to determine if equality in access to care is ensured.
5) Acquire data on registry use in Hungary and internationally, as registries are a preliminary base for epidemiological studies, and hypothetically they can also serve as quality control tools for National Health Institutes.

III. Patients and Methods

III.1. Do Hungarian multiple sclerosis care units fulfil international criteria?

In 2019, considering the international MSCU recommendations, the DSNS advised the foundation of National Multiple Sclerosis Symposiums to assess whether currently ongoing MS management fulfils international standards. The assessment was conducted at the Department of Neurology, University of Szeged, Albert Szent-Györgyi Health Centre, Szeged, Hungary. A self-reported questionnaire surveying personnel and infrastructural criteria of MSCUs, according to the ECTRIMS/EAN and MSCU recommendations was assembled and sent to Hungarian MS centres. The questionnaire consisted of 3 main parts, of which the first focused on patient number, the second surveyed 22 aspects of the MSCU recommendation (Table 2).

MS care unit criteria – detailed questionnaire	
Minimum requirements of a multidisciplinary MS care unit	**Available in the MS care unit**
Core of the MS care unit	
Number of persons with MS receiving care	_____
Number of MS neurologists	_____
MS nurse	☐ Yes / ☐ No
Secretary / Administrator	☐ Yes / ☐ No
Collaboration with part-time specialists	
Neuropsychologist	☐ Yes / ☐ No
Pharmacist with special knowledge of DMTs	☐ Yes / ☐ No
Dietitian	☐ Yes / ☐ No
Speech therapist	☐ Yes / ☐ No
Pain specialist	☐ Yes / ☐ No
Continence specialist	☐ Yes / ☐ No
Spasticity specialist	☐ Yes / ☐ No
Recommended requirements to achieve a fully developed multidisciplinary MS care unit	**Available in the MS care unit**
Collaboration with other specialties	
Radiology with MS-familiar neuro-radiologist	☐ Yes / ☐ No
Microbiology	☐ Yes / ☐ No
Laboratory	☐ Yes / ☐ No
Electrophysiology	☐ Yes / ☐ No
Ophthalmology	☐ Yes / ☐ No
Physician / Internal medicine specialist	☐ Yes / ☐ No
Surgeon	☐ Yes / ☐ No
Neurosurgeon	☐ Yes / ☐ No
Obstetrician gynaecologist	☐ Yes / ☐ No
Neuro-ophthalmologist	☐ Yes / ☐ No
Neuro-otologist	☐ Yes / ☐ No
Psychiatrist	☐ Yes / ☐ No
Neurorehabilitation	☐ Yes / ☐ No

Table 2: Questionnaire regarding patient number and aspects of the international MS care unit criteria

Abbreviations: MS = multiple sclerosis

While the third section of the questionnaire assessed DMT and registry use (Table 3).

Currently available DMTs in the MS care unit			
For low disease activity	For high disease activity	For very high disease activity	Other
☐ Interferon-β	☐ Natalizumab	☐ Alemtuzumab	☐ Mitoxantrone
☐ Glatiramer acetate	☐ Fingolimod	☐ Ocrelizumab	☐ Azathioprine
☐ Dimethyl fumarate		☐ Cladribine	☐ Cyclophosphamide
☐ Teriflunomide			☐ Siponimod
Registry use			
Does the MS care unit participate in data entry into an international registry?			☐ Yes / ☐ No
Does the MS care unit participate in data entry into a national registry?			☐ Yes / ☐ No
Does the MS care unit participate in data entry into a regional registry?			☐ Yes / ☐ No

Table 3: Third section of the questionnaire focusing on currently available DMTs and registry use of the MS care unit

Abbreviations: DMT = disease modifying therapy, MS = multiple sclerosis

In the original MSCU article the "core of the MSCU" criteria were referred to as "minimum criteria" in our survey. The minimum criteria consisted of: MS nurse, secretary/administrator, pharmacist, dietitian, neuropsychologist, speech therapist, pain specialist, continence specialist, and spasticity specialist. In the original MSCU article the "fully developed MSCU" criteria were referred to as "recommended criteria" in our survey. Recommended criteria included: neuro-radiologist, microbiology, laboratory, electrophysiology, ophthalmology, physician/internal medicine specialist, surgeon, neurosurgeon, obstetrician-gynaecologist, neuro-ophthalmologist, oto-neurologist, psychiatrist, and neurorehabilitation. It is important to note, that minimum criteria include strictly MS-peculiar specialities, that distinguish MS specific care from non-MS specific care. Thus, even though the term "minimum criteria" might imply that those are easier to fulfil, the reality might be the opposite. On the other hand, "recommended criteria" include less specific personnel and instrumental conditions, that rather play an important role in the diagnosis of MS and management of comorbidities, thus those might be more commonly available.

Data collection began on November 1, 2020, and ended on January 31, 2021. NHIF data was also collected regarding DMT use of December 2020 to obtain a thorough overview on the proportion of low/moderately and highly effective DMT use.

We used descriptive statistics to analyse data.

The study was approved by the Hungarian Medical Research Council, reference number: IV/5139-1/2021/EKU. The study was conducted in accordance with the Declaration of Helsinki.

III.2. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants

The study was conducted at the Department of Neurology, University of Szeged, Albert Szent-Györgyi Health Centre, Szeged, Hungary. Besides Hungary further 8 DSNS member countries participated: Austria, Croatia, Czech Republic, Poland, Romania, Serbia, Slovakia, and Slovenia. As a reference two further centres from Denmark and Germany also engaged in supplying data. The MSCU questionnaire used in the Hungarian study was translated to English and was sent to participating countries' MS centres via e-mail. Information on management of MS, DMT reimbursement and prevalence estimates were collected parallelly. Data acquisition began in December 2020 and ended in December 2021.

We used descriptive statistics to summarise and analyse data. We included completely and incompletely filled questionnaires as well.

Homogeneity and heterogeneity were defined by calculating the percentage of centres in each country that fulfilled each criterion. Percentages were then divided into four quadrants (Q1-Q4). If a criterion was fulfilled by 76-100% of care units, it reached Q1 level. If it was ensured by 51-75% of centres, it was indicated as Q2 level. If it was available in 26-50% of centres, it reached Q3 level, and if it was fulfilled in 0-25%, it was indicated as Q4 level. Then, Q1-Q4 levels were further aggregated into three main categories: homogenous availability, slightly heterogenous availability and high heterogeneity. Homogenous availability was only disclosed if 9/9 participating countries reached Q1 level in the fulfilment of the criterion. Slightly heterogenous availability was disclosed if 1-3 county's centres reached only Q2-Q4 levels in the fulfilment of the criterion. High heterogeneity was disclosed if 4 or more country's centres reached only Q2-Q4 levels in the fulfilment of the criterion.

Most up-to-date prevalence estimates were searched in several research tools and most recent population data were collected in March 2022. The "number of patients according to prevalence estimates" was determined by utilizing the following formula:

$$\frac{current\ population\ (number\ of\ people\ in\ the\ country)}{100\ 000} \times most\ recent\ prevalence\ data\ (number\ of\ cases\ per\ 100\ 000\ people)$$

These results were then compared to the actual number of patients reported by centres, resulting in the "difference between estimated and the actual number of patients" utilizing the following formula:

$$number\ of\ patients\ according\ to\ prevalence\ data\ (number) - Number\ of\ patients\ reported\ by\ centres\ (number)$$

The study was approved by the Hungarian Medical Research Council (reference number IV/5139-1/2021/EKU) and conducted in accordance with the Declaration of Helsinki.

IV. Results

IV.1. Do Hungarian multiple sclerosis care units fulfil international criteria?

IV.1.a. Participation rate

In our survey 29/31 Hungarian MS centres participated, equalling a 94% participation rate, which is considered representative. Nevertheless, only 24/29 MSCUs filled out every section of the questionnaire. Since the different sections are not directly connected to each other, sections could be interpreted separately, thus we included completely and partially filled question sheets as well. In the analysis MSCUs were numbered instead of using hospital names, to ensure anonymity.

IV.1.b. Personnel and instrumental background of MS care units

There were 26/29 MSCUs that provided information on MS neurologist number. In these 26 centres 86 MS neurologist provided care for people living with MS. The median number of MS neurologists was 3/care unit (range 1-8). Regarding MS care unit criteria 27/29 centres filled out the questionnaire. The employment of at least one MS nurse was reported by 26/29 centres, there was 1 care unit that did not employ an MS nurse. In 21/29 centres at least one administrator was employed, ensuring fast, precise administration of patient documentation. Regarding spasticity (13/29), pain specialist (15/29), neuro-ophthalmologist (15/29), oto-neurologist (15/29), neuropsychologist (19/29), and speech therapist (21/29) greater shortcomings were reported. Neurorehabilitation was not ensured in 5/29 centres, 3/29 MSCUs did not employ an MS radiologist, in 2/29 care units an MRI was not available. In total 3/29 centres fulfilled both minimum and recommended criteria, while further 7 care units provided all aspects of recommended criteria only (Figure 4).

Organization of the MS care units		Hungarian multiple sclerosis care units numbered from 1 to 29																											Summary	
		1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	Total	%
Minimum requirements of a multidisciplinary MS care unit	Core	Number of persons with MS	150	92	320	N/A	400	500	269	40	415	400	119	200	400	240	196	200	400	53	250	411	88	950	120	70	122	250	348	210	N/A	7213	N/A
		Number of MS neurologists	5	2	4	N/A	2	5	2	2	6	6	3	2	4	3	2	2	1	N/A	3	8	1	7	3	1	3	2	5	2	N/A	86	N/A
		MS nurse	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X		X	N/A	X	X	X	26	89.66%
		Secretary		X	X		X	X		X	X	X	X	X	X	X	X		X	X	X	X	N/A	X	X		X	N/A	X	X	X	21	72.41%
	Collaboration with part-time specialists	Neuropsychologist	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X			N/A	X	X		19	65.52%
		Pharmacist	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Dietitian	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Speech therapist	X		X		X	X	X	X	X	X	X	X	X	X	X		X		X	X	N/A	X	X	X	X	N/A	X	X		21	72.41%
		Pain specialis		X	X	X	X	X			X	X	X					X			X	X	N/A	X	X			N/A	X	X		15	51.72%
		Continence specialist	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	25	86.21%
		Spasticity specialst			X		X	X		X	X	X	X					X	X	X	X	X	N/A	X	X			N/A		X		13	44.83%
Recommended to achieve the fully developed multidisciplinary MS care unit	Collaboration with other specialties	MS-familial neuro-radiologist	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	24	82.76%
		Microbiology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Laboratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Electrophysiology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	N/A	X	X	X		N/A	X	X	X	25	86.21%
		Ophtalmology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Physician	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Surgeon	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	25	86.21%
		Neurosurgeon	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	N/A	X	X		X	N/A	X	X		23	79.31%
		Obstetrician gynecologist	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	25	86.21%
		Neuro-ophtalmologist		X	X		X	X	X	X	X	X	X							X	X	X	N/A	X				N/A	X	X		15	51.72%
		Otoneurologist	X		X			X		X	X	X	X	X	X					X	X	X	N/A	X				N/A	X	X		15	51.72%
		Psychiatrist	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X	X	N/A	X	X	X	27	93.10%
		Neurorehabilitation	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	N/A	X	X		X	N/A		X		22	75.86%
Summary		Number of missing criteria	4	4	3	7	1	0	6	3	1	0	0	4	3	6	5	7	4	0	0	0	N/A	0	2	10	7	N/A	2	0	8		
		Minimum criteria fulfilled					X	X			X	X	X							X	X	X	N/A	X	X			N/A		X		10	34.48%
		Recommended criteria fulfilled						X				X	X							X	X	X	N/A	X				N/A		X		7	24.14%
		Both fulfilled						X				X	X							X	X	X	N/A	X				N/A		X		7	24.14%

Figure 4: Fulfilment of multiple sclerosis care unit criteria among Hungarian MS centres

Abbreviations: MS = multiple sclerosis, N/A = no data available

Participating centres are numbered consecutively from 1-29, the letter "X" indicates fulfilled criteria, while grey coloured cells suggest that the criterion was not fulfilled.

IV.1.c. DMT use in MS care units

There were 27/29 care units that filled out the part of the questionnaire on DMT use. Low/moderately effective DMTs were used in all of the respondent centres. However, highly effective treatment use rate was lower. Only in 20/29 centre was every highly effective treatment option available. In 1/29 centres out of the oral highly effective DMTs (HEDMTs) only cladribine (CLA) was ensured, in 5/29 care units solely fingolimod (FG) was available. Regarding infusion therapies, 1/29 centres administered natalizumab (NAT) and alemtuzumab (ALM), while 1/29 care unit ensured solely ocrelizumab (OCR) and 1/29 centre used ALM only. In 3/29 centres none of the infusion therapies were available. In total 15/29 centres administered the entire spectrum of DMTs (Table 4).

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.
IFN	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X
DMF	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X
GA	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X
TFL	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	X	X	X
FG	X	X	X	N/A	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	N/A	X	X	X
CLA	X	X	X	N/A	X	X		X	X	X	X	X	X		X	X	X		X	X		X			X	N/A	X	X	X
NAT	X	X	X	N/A	X	X	X		X	X	X	X	X		X	X	X		X	X		X	X	X		N/A	X	X	X
ALM	X		X	N/A	X	X	X		X		X		X		X	X	X		X	X		X			X	N/A	X	X	X
OCR	X	X	X	N/A	X	X	X	X	X	X	X	X	X		X	X	X		X	X		X	X	X		N/A	X	X	

Table 4: Disease modifying therapy use among participating care units

Abbreviations: ALM = alemtuzumab, CLA =cladribine, DMF = dimethyl fumarate, FG = fingolimod, GA = glatiramer acetate, IFN = interferon-β, NAT = natalizumab, N/A = no data available, OCR = ocrelizumab, TFL = teriflunomide

The first row includes participating care units numbered from 1-29, the letter "X" implies that the DMT is ensured, black coloured cells suggest the absence of the DMT, medium grey columns indicate care units that provide the whole therapeutic arsenal.

IV.1.d. Proportion of moderately and highly effective DMT use

Regarding number of people on DMTs in, NHIF data in December 2020 showed that 4 665 persons received MS specific treatment. Of these people 3 131 (67.12%) used low/moderately effective DMTs. Of the low/moderately effective DMT users, 1 360 (43.44%) persons were injectable therapy users, and 1 771 (56.56%) patients were on oral agents. Consequently, solely 1 534 (32.88%) people were on HEDMTs, of which 810 (52.80%) persons used oral medication, and 724 (47.20%) patients received infusions.

IV.1.e. Patient number receiving care in MS care units

In total 27/29 centres provided information on patient number, which showed great differences among care units. In the 27 centres 7 213 people received MS specific care, with a median number of 240/care unit (range 40-950). Majority of medical care of pwMS occurred in 8 facilities: 4 University Departments, 2 county hospitals and 2 general hospital ensured care of 3 876 (53.74%) patients. Further 10 facilities cared for 2 483 (34.42%) people (range 196-348). While the remaining 854 (11.84%) persons (range 40-150) received care in the remaining 9 hospitals (Figure 5).

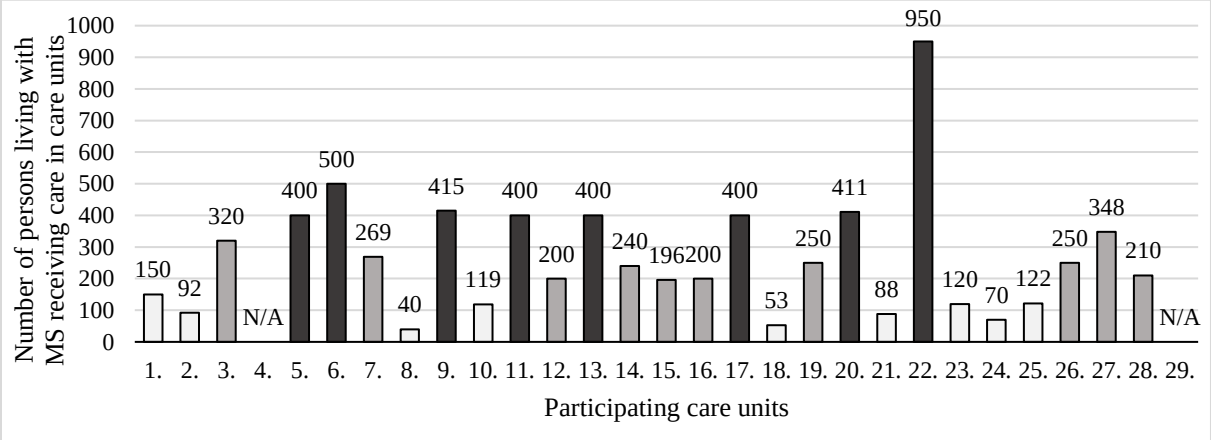

Figure 5: Distribution of people living with MS receiving care in multiple sclerosis centres

Abbreviations: MS = multiple sclerosis, N/A = no data available

Participating centres are numbered consecutively from 1-29, the columns are colour-coded to represent three distribution categories: light grey for low, medium grey for moderate, and dark grey for high patient number.

IV.2. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants

IV.2.a Participation rate

From the participating 9 DSNS countries, we received a total of 101 questionnaires, furthermore 1-1 Danish and German reference surveys. In Austria, the participation rate can be considered 100%. Since the 3 questionnaires received, represent 2 University Departments and the Austrian Centre Network, consisting of 132 individual care units, which is a system rigorously regulated by the Austrian Society of Neurology (ASN). In addition, Romanian (15/15) and Serbian (5/5) participation rate was 100% as well. The participation rate in Hungary, Slovakia, Slovenia, and the Czech Republic was still considerably high, 94% (29/31), 90% (9/10), 67% (2/3) and 60% (9/15) respectively. Whereas only 50% (5/10) of Croatian and 19% (24/129) of Polish care units filled out our survey.

IV.2.b. Management of multiple sclerosis and disease-modifying therapy reimbursement in participating countries

Management of people living with MS was pursued in specialized MS care units in all participating countries. Furthermore, every available DMT was reimbursed by National Health Insurance Funds. To regulate DMT prescription, firstly, Hungary established MS centre conditions in 1996, followed by the Czech Republic in the same year (redefined in 2019), and Austria in 2000 (updated in 2014). In the latter two countries, management of MS is strictly regulated, certified MS care units may only operate if they fulfil predefined conditions. In Denmark and Germany, a similar approach is pursued as well (Table 5,6).

	Management of multiple sclerosis, registry use and disease-modifying therapy reimbursement
Austria	**1) Since 2000, people with MS (pwMS) have received medical care in the Austrian Centre Network.** The latest version of the MS Centre Network Conditions was composed in 2014. Currently, the Centre Network consists of 132 centres, which Network is strictly regulated by the Austrian Society of Neurology (ASN). Conditions to become a centre: - The head of the institute should be a neurologist with expertise in the field of MS. - Knowledge of the latest clinical, diagnostic, and therapeutic guidelines, capability to perform a standard neurologic examination supplemented with Expanded Disability Status Scale (EDSS) scores, and capability to interpret magnetic resonance imaging (MRI) results should be ensured. - Capability to treat pwMS according to the latest therapeutic guidelines. - Personnel and instrumental conditions should be guaranteed (medical assessment within 14 days, relapse treatment within 48 hours, at least 60-minute-long therapeutic visits, separate examination room, room to collect cerebrospinal fluid (CSF) samples, infusion room, waiting room etc.). - As centres are part of a network, treatment of other aspects of the disease is ensured. - Documentation should include patient history, EDSS, MRI results, therapeutic indication, relapses, adherence to therapy. - Application to obtain centre status should be filed in writing to the ASN, including evidence that the conditions described above are fulfilled. Certification needs to be renewed every 2 years. - Regular participation in MS training and Centre Network conferences is mandatory. **2) Data entry of pwMS receiving DMTs is mandatory into the Austrian Treatment Registry.** **3) DMTs are available free of charge.**
Croatia	**1) Medical care of pwMS is pursued in 10 specialized institutes.** Diagnostic and therapeutic guidelines are accessible on the website of the Croatian Association of Neurology. Different DMTs can be commenced if pwMS fulfil initiation criteria: - EDSS scores are in the therapeutic range of the DMT. - Disease activity is in the therapeutic range of the DMT. - Approval of the institutional pharmacy to begin treatment is ensured. **2) A national registry is not available, and centres record data on a voluntary basis.** **3) DMTs are available free of charge.**

Czech Republic	**1) Medical care of people with MS (pwMS) is ambulatory and takes place in specialized centres.** In severe cases, the centre should provide inpatient care: either the centre itself guarantees the appropriate conditions or it is in close contact with a hospital to which pwMS can be referred to. A system of specialised MS centres was established in the Czech Republic in 1996, but the main aim of this system was to control the prescription of DMTs. Thanks to the systematic efforts of the Neurological Society, an agreement was then reached with the Ministry of Health Institute in 2019, and the conditions to become a highly specialised care centre or to maintain this status were redefined, with a focus on the latest applicable diagnostic and therapeutic guidelines. Currently, 15 centres are responsible for the medical care of pwMS, and the number of centres is maximized, it may not exceed 17. Application to achieve the centre status should be filed in writing to the Czech Ministry of Health, including evidence that the conditions mentioned above are fulfilled, and quality control should be ensured. The Czech Health Care Provider regularly monitors quality indicators of the centres, including: - Availability of a highly specialized medical staff: On one hand a multidisciplinary team with working hours adjusted to patient number should be ensured. Additionally, the head of the institute should be a board-certified neurologist. - Number and proportion of patients receiving DMT. - Instrumental background: magnetic resonance imaging (MRI), optical coherence tomography (OCT), evoked potential tests, cerebrospinal fluid (CSF) analysis, laboratory, examination room and infusion room should be ensured. Furthermore, the number of infusion pumps should be adjusted to patient number. - All treatment options should be available. - Centre status certification should be renewed every 5 years and in case of changing conditions, the Czech Ministry of Health should be notified in writing. **2) Since 2013 patient data should be recorded in the Czecz Registry of Patients with Multiple Sclerosis (ReMus)**, from which annual reports, and regular epidemiological and financial statistics can be obtained. **3) DMTs are available free of charge.**
Hungary	Specialized MS centre conditions were established by the Hungarian Neurological Professional College in 1996: - The designated hospitals' neurological departments should provide a separate outpatient unit dedicated to pwMS, granting a minimum of 6 consulting hours/week. - The institute where the centre is located, should have the conditions to examine, diagnose, and treat pwMS. - The MS care team should consist of at least 2 neurologists experienced in the field of MS and one specially trained MS nurse. - Documentation should include patient history, annualized relapse rate (ARR) during DMT, and physical status including Expanded Disability Status Scale (EDSS). These conditions were determined over 20 years ago due to the high retail price interferon-beta (IFN-β). Since treatment resources were limited, the insurance would only fund treatment under strictly regulated and regularly monitored conditions. However, these criteria have not evolved in accordance with the changing circumstances experienced in the past years. **1) Currently 31 centres are responsible for the medical care of pwMS**, 11 hospitals located in the capital city and generally 1-1 located in each county. MS centres are responsible for the medical care of pwMS in their region. **2) Patient documentation is not standardized, and a national registry is not available.** However, the regional registry of Szeged and the G35H0 and the International Classification of Diseases 10th edition (ICD-10) codes were used for prevalence estimates. **3) DMTs are available free of charge.**

Poland	**1) In Poland management of MS is undertaken in 129 centres** (65 specialised MS centres and 64 general MS centres with more or less even regional distribution in 16 voivodeships). - Specialised MS centres provide the full spectrum of Ist and IInd line drugs, and in total, are based within regional hospital facilities, while general MS centres provide basic diagnostic options and manage patients using first-line drugs. - Mostly, MS management is carried out in outpatient units, with regular access to hospital wards. - The Polish Neuroscience Society (PolNS) provides training, and conferences in MS and is responsible for developing diagnostic and therapeutic guidelines, and epidemiological analyses. **2) A national registry is available in Poland**, with a two-sided data platform (MS neurologists and patients can also enter data); however, data entry is voluntary. **3) DMTs are available free of charge.** All drugs are dispensed within state-funded treatment programmes based on locally calculated budgets.
Romania	**1) Medical care of people with MS (pwMS) is pursued in specialized centres.** Past-present: - 15 centres were responsible for the care of pwMS, 9 located in the capital city; thus, regional care of patients was not possible, resulting in inequality in access to treatment. - Due to the more advanced technical and personnel background, mainly university hospitals were designated as centres; however, rehabilitation was not solved in most of them. - A general practitioner (GP) referred suspected MS cases to a neurologist, who referred the patient to an MS centre, and only neurologists experienced in MS could request diagnostic tests. - High costs of diagnostic tests and limited financial resources, absence of standard magnetic resonance imaging (MRI) protocols, and shortage of neuroradiologists lead to delays in the diagnosis. - MS neurologists and in some cases general neurologist provided medical care for pwMS. Present-future (recently published MS centre conditions): - Provides an opportunity for accreditation for all county hospitals; thus, the number and distribution of MS centres should ensure equality of access to care. - Suggests that multidisciplinary care should be adapted to outpatient care (it was usually solved within the framework of inpatient care, resulting in more costs). - Advocates the development of rehabilitation opportunities. - Suggests the regular use of the national registry. **2) A national registry is available with voluntary data entry.** **3) DMTs are available free of charge.**
Slovakia	**1) Management of pwMS is pursued in 10 specialized centres.** **2) A national registry is available with voluntary data entry.** **3) DMTs are available free of charge.**
Slovenia	**1) Management of pwMS is pursued in 3 MS centres**, however there is a shortage of MS nurses and neurologists specialized in MS. **2) A national registry is not available.** **3) DMTs are available free of charge.**
Serbia	**1) Management of MS is pursued in 5 MS centres.** **2) A national registry is not available** **3) DMTs are available free of charge.**

Table 5: Management of multiple sclerosis, registry use and disease-modifying therapy reimbursement in Danube Symposium for Neurological Sciences countries

Abbreviations: ARR = annualized relapse rate, ASN = Austrian Society of Neurology, CSF = cerebrospinal fluid, DMT = disease modifying therapy, EDSS = Expanded Disability Status Scale, GP = general practitioner, ICD-10 = International Classification of Diseases 10th edition, IFN-β = interferon beta, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCT = Optical Coherence Tomography, PolNS = Polish Neuroscience Society, pwMS = people with multiple sclerosis, ReMus = Czecz Registry of Patients with Multiple Sclerosis

	Management of multiple sclerosis, registry use and disease-modifying therapy reimbursement
Denmark	The country is divided into four main regions with different health care system and financial background. **1) Management of MS is pursued in 13 MS clinics**, the only units authorized to prescribe DMTs. MS clinics predominantly provide outpatient care for people with MS (pwMS). However, when inpatient care is needed, hospitalization of patients is ensured by close collaboration with inpatient departments. **2) Use of the national Danish Multiple Sclerosis Registry is mandatory for all centres.** **3) DMTs are available free of charge**, and it is the Danish Medicines Council's role to provide national treatment recommendations.
Germany	**1) Management of MS is pursued in 187 centres** (70 specialized MS centres, 95 general MS centres, and 22 MS rehabilitation centres), certified by the German Multiple Sclerosis Society (DMSG). However, DMSG certification is voluntary, and it is not necessary to provide MS care and receive reimbursement for medications. Centre types operate under specified conditions, determined by the DMSG, consisting of 4 main sections: • Expertise and training ◦ Continuous management of pwMS should be performed by board-certified neurologists who have at least 5 years of experience, also other healthcare professionals should have at least 2 years of experience in MS care. ◦ Regular training and education opportunities should be ensured for MS neurologists, healthcare professionals, and neighbouring specialties partaking in the management of MS. ◦ The pre-determined minimum number of patients managed in outpatient and inpatient facilities is established (specific to each centre category). MS centres should manage at least 80-120 pwMS, while specialized MS centres and MS rehabilitation centres should care for at least 400 and 120 pwMS, respectively. • Diagnostics ◦ The very first consultation at the centre should last for at least 1 hour. ◦ Patient examination, assessment of physical status, determination of deficits, and evoked potential tests should be executed and documented according to standardized manners. ◦ Cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) should be conducted by certified personnel using standardized protocols in general and specialized MS centres. • Management of MS ◦ MS centres and specialized MS centres ▪ Criteria of diagnostic and therapeutic guidelines should be fulfilled and implemented. ▪ Treatment with DMTs and relapse treatment should be ensured. ▪ Symptomatic treatment (management of bladder dysfunction) and rehabilitation (physiotherapy, ergotherapy, speech therapy) of pwMS should be ensured. ◦ MS rehabilitation centres ▪ Physiotherapy, occupational therapy, speech therapy, and consultation with a psychologist and neuropsychologist should be ensured. ▪ Consultations regarding disease information, coping strategies, and self-catheterization should be ensured. Furthermore, consultation with social workers and the supply of medical aids should be guaranteed. **2) A national registry – called German Multiple Sclerosis Registry – is available.** **3) DMTs are available free of charge**.

Table 6: Management of multiple sclerosis, registry use and disease-modifying therapy reimbursement in Denmark and Germany

Abbreviations: CSF = cerebrospinal fluid, DMSG = German Multiple Sclerosis Society, DMT = disease modifying therapy, MRI = magnetic resonance imaging, MS = multiple sclerosis, pwMS = people with multiple sclerosis

IV.2.c. Multiple sclerosis care unit criteria

The section of the questionnaire surveying MSCU criteria was filled out by 97/103 centres. While 2/29 Hungarian, 1/24 Polish and 1/9 Slovakian centres did not fill out this part of the questionnaire, and 3/24 Polish and 1/5 Croatian care units provided incomplete information.

The Austrian MS Centre Network and 2 University Departments fulfilled both the minimum and recommended criteria.

Among Croatian centres, 1/5 provided all aspects of the minimum and recommended conditions, in the rest of the care units either secretary, spasticity or pain specialist was not ensured, thus minimum criteria were not fulfilled. Recommended conditions were provided by 2/5 centres, while in 1/5 care unit no oto-neurologist was employed.

In total 5/9 Czech care units fulfilled minimum and recommended conditions, 1/9 centre ensured all aspects of minimum criteria only. In the rest of the facilities either microbiology, speech therapist, continence and pain specialist, or oto-neurologist was not employed.

Approximately one third (10/29) of the Hungarian care units fulfilled minimum conditions, of which 7/29 provided all aspects of recommended criteria as well. Most common insufficiencies were neuropsychologist, spasticity and pain specialist, oto-neurologist, and neuro-ophthalmologist.

Among Polish centres 2/24 fulfilled both minimum and recommended conditions, 2/24 provided all aspect of the minimum criteria only, while further 5/24 facilities fulfilled recommended conditions only. In the rest of the care units either secretary, microbiology, continence, spasticity, or pain specialists were missing.

According to Romanian questionnaires, only 1/15 care units fulfilled recommended criteria, the rest of the centres did not ensure secretary, ophthalmology, speech therapist, pain, continence, and spasticity specialist, neurosurgeon, obstetrician-gynaecologist, neuro-ophthalmologist, and oto-neurologist.

Out of the Serbian centres 1/5 ensured all aspect of minimum and recommended conditions, while 2/5 care units provided all aspect of recommended criteria only. In the rest of the facilities secretary, speech therapist, continence specialist, spasticity specialist and neuro-ophthalmologist were commonly absent.

In total 3/9 Slovakian centres fulfilled recommended criteria. Secretary, neuropsychologist, speech therapist, pain, continence, and spasticity specialist, ophthalmology, neurorehabilitation, surgeon, neuro-ophthalmologist, oto-neurologist, and psychiatrist were not consistently ensured in the rest of the facilities.

Neither of the respondent Slovenian care units (0/2) fulfilled every aspect of the minimum or the recommended conditions. Pain, continence, and spasticity specialist, surgeon, oto-neurologist, electrophysiology, and ophthalmology were the least prevalent specialties.

In the Danish and German reference centres all aspects of minimum and recommended criteria were ensured.

Regarding the fulfilment of minimum and recommended conditions homogeneities and heterogeneities were discovered. To sum up the above detailed information, in 4/9 countries more than 75% of the ensured at least 75% of the conditions, providing homogenous availability of criteria. On the other hand, care units in the other countries provided heterogenous availability of conditions. In one hand, MS nurse, pharmacist, dietitian, neuroradiologist, laboratory, internal medicine specialist, psychiatry, and neurorehabilitation were homogenously available. On the other hand, the availability of neuropsychologist, microbiology, electrophysiology, ophthalmology, surgeon, neurosurgeon, and obstetrician-gynaecologist showed slight heterogeneity among countries. With that said, the availability of administrator, speech therapist, pain, continence, and spasticity specialist, oto-neurologist, and neuro-ophthalmologist was highly heterogenous (Figure 6).

	Au	Cr	Cz	Hu	Pl	Ro	Srb	Sk	Slo	
MS nurse	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Secretary	Q1	**Q2**	Q1	**Q2**	**Q2**	**Q2**	**Q2**	**Q4**	Q1	High heterogeneity in the availability among countries
Neuropsychologist	Q1	Q1	Q1	**Q2**	Q1	Q1	Q1	Q2	Q1	Slightly heterogenous availability among countries
Pharmacist	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Dietitian	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Speech therapist	Q1	Q1	Q1	**Q2**	**Q2**	**Q3**	**Q3**	**Q3**	Q1	High heterogeneity in the availability among countries
Pain specialist	Q1	Q1	Q1	**Q2**	**Q3**	**Q4**	Q1	**Q3**	**Q4**	High heterogeneity in the availability among countries
Continence specialist	Q1	Q1	Q1	Q1	**Q3**	Q4	Q2	**Q3**	**Q4**	High heterogeneity in the availability among countries
Spasticity specialist	Q1	**Q3**	Q1	**Q3**	**Q2**	**Q4**	**Q3**	**Q4**	**Q2/Q3**	High heterogeneity in the availability among countries
Neuro-radiologist	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Microbiology	Q1	Q1	Q1	Q1	**Q2**	Q1	Q1	**Q2**	Q1	Slightly heterogenous availability among countries
Laboratory	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Electrophysiology	Q1	Q1	Q1	**Q2**	Q1	Q1	Q1	Q1	**Q2/Q3**	Slightly heterogenous availability among countries
Ophthalmology	Q1	Q1	Q1	Q1	Q1	**Q2**	Q1	Q1	**Q2/Q3**	Slightly heterogenous availability among countries
Internal medicine	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Q1	Homogenously available in 9/9 countries
Surgeon	Q1	Q1	Q1	Q1	**Q2**	Q1	Q1	**Q2**	**Q2/Q3**	Slightly heterogenous availability among countries
Neurosurgeon	Q1	Q1	Q1	Q1	**Q2**	**Q2**	Q1	Q1	Q1	Slightly heterogenous availability among countries
Obstetrician-	Q1	Q1	Q1	Q1	**Q2**	**Q2**	Q1	Q1	Q1	Slightly heterogenous availability among countries
Neuro-ophthalmologist	Q1	Q1	Q1	**Q2**	Q1	**Q3**	**Q2**	**Q2**	Q1	High heterogeneity in the availability among countries
Oto-neurologist	Q1	Q1	**Q2**	**Q2**	**Q2**	**Q4**	Q1	**Q2**	**Q2/Q3**	High heterogeneity in the availability among countries
Psychiatrist	Q1	Q1	Q1	Q1	Q1	Q1	Q1	**Q2**	Q1	Homogenously available in 9/9 countries
Neurorehabilitation	Q1	Q1	Q1	Q1	Q1	Q1	Q1	**Q2**	Q1	Homogenously available in 9/9 countries
Q1 percentile proportion	100%	90%	95%	**63%**	**55%**	**55%**	77%	**45%**	**68%**	In 4/9 countries ≥ 75% of MSCUs fulfilled ≥ 75% of the criteria (Q1). In 5/9 countries 7-12 criteria were heterogeneously fulfilled (Q2-4). Homogeneous shortcomings were: administrator, speech therapist, pain, continence, and spasticity specialist, oto-neurologist, and neuro-ophthalmologist.
Q2 percentile proportion	0%	5%	5%	**32%**	**36%**	**18%**	14%	**32%**	**23%**	
Q3 percentile proportion	0%	5%	0%	**5%**	**9%**	**9%**	9%	**14%**		
Q4 percentile proportion	0%	0%	0%	**0%**	**0%**	**18%**	0%	**9%**	**9%**	

Figure 6: **Homogeneity and heterogeneity regarding the fulfilment of the multiple sclerosis care unit criteria characterized by quadrantile levels**

Abbreviation: Au = Austria, Cr = Croatia, Cz = Czech Republic, Hu = Hungary, MS = multiple sclerosis, MSCU = multiple sclerosis care unit, Pl = Poland, Ro = Romania, Srb = Serbia, Sk = Slovakia, Slo = Slovenia

Q1 (white cells): first quadrant – 100-76% of centres fulfil the criteria, Q2 (light grey cells): second quadrant – 75-51% of centres fulfil the criteria, Q3 (medium grey cells): third quadrant – 50-26% of centres fulfil the criteria, Q4 (dark grey cells): fourth quadrant – 25-0% of centres fulfil the criteria

IV.2.d. DMT use

Regarding DMT use 96/103 care units provided information. Whereas, 1/9 Czech, 2/29 Hungarian, 1/24 Polish, 1/15 Romanian, and 2/9 Slovakian centres did not fill out this part of the questionnaire. The entire arsenal of DMTs were administered in all Austrian, and respondent Slovenian and Slovakian care units. Nonetheless, in some centres of the remaining countries one or several DMTs were not provided. In 1/5 Croatian centre NAT was not accessible, in 1/9 Czech centre CLA was not used, in 1/5 Serbian centres dimethyl fumarate (DMF) and NAT were not administered, while the rest of the facilities of these countries provided the entire spectrum of DMTs. Approximately half (15/29) of Hungarian and two-thirds (16/24) of Polish centres ensured every DMT. Romanian care units rarely administered DMF and ALM, and did not use CLA at all, as it was not approved by the Romanian Mediation Authorities at the time of the inquiry. The Danish and German reference centres provided all available DMTs.

IV.2.e. Patient number, prevalence estimates

In total 99/101 centres provided information on patient number, thus ensuring care for 74 937 patients cumulatively. The Danish and German reference centres reported the management of further 4 000 and 2 000 people respectively. When comparing actual patient number reported by countries to estimated patient number according to prevalence estimates a substantial difference was detected in countries where participation rate was low. Since this could influence conclusions driven from these data, this phenomenon was taken into consideration during evaluation. Evidently, in the instance of Slovakia, where no prevalence estimate was published, and in Denmark and Germany, where only 1-1 reference centres participated, thus representativity was not ensured, no comparisons were implemented. Nevertheless, in the assessment of the proportion of patients receiving adequate care, this method could still be considered practical. According to our comparison, only Austrian and Czech result were congruent, where mandatory national registry use was reported, detailed below. Whereas results in other countries were discrepant, which, besides low participation rates, could be explained by the lack of either mandatory registry use or up-to-date prevalence data (Figure 7).

	Population in 2022	Prevalence /100 000 inhabitants	Methodology and date of the latest prevalence estimate	Number of patients according to prevalence estimates	Number of patients reported by centres	Difference between the estimated and reported number of patients	The proportion of the participating centres / total number of centres
Austria	9 006 000	158.9	based on ICD-10 codes, 2017	14 310	14 500	+190	3/3 (including one covering the entire Austrian MS Centre Network)
Croatia	4 105 000	143.8	based on three national patient registries and data from the MS patient organization, 2018	5 903	4 350	-1 553	5/10
Czech Republic	10 709 000	187	based on the Czecz Registry of Patients with Multiple Sclerosis (ReMus), 2020	17 485	12 400	-5 085	9/15
Hungary	9 660 000	101.8 130.8	based on regional registry data, 2020 based on ICD-10 codes, 2020	9 833 12 635	7 213	-2 620 -5 422	29/31
Poland	37 846 000	109.1 (120)	based on regional data, 2018 (based on the Atlas of MS, 2020)	41 289 (45 415 Atlas of MS)	16 015	-25 274 (-29 400 Atlas of MS)	24/140
Romania	19 237 000	53.6 (35)	based on ICD-10 codes, 2015 (based on the Atlas of MS, 2020)	10 311 (6 732 Atlas of MS)	5 255	-5 056 (-1 477 Atlas of MS)	15/15
Serbia	8 737 000	136.8	based on ECTRIMS online library data, 2019	11 952	6 570	-5 382	5/5
Slovakia	5 459 000	N/A	N/A	N/A	4 834	not interpretable	9/10
Slovenia	2 078 000	151.9	based on regional registry data, 2006	3 156	3 800	+643	2/3
Denmark	5 792 000	284	based on the Danish Multiple Sclerosis Registry (DMSR), 2020	17 747 (most recent, not published data from the DMSR)	4 000	not interpretable	1/13
Germany	84 225 000	303	based on the German Multiple Sclerosis Registry (GMSR), 2020	252 000 (data from GMSR)	2 000	not interpretable	1/187

Figure 7: Patient numbers according to prevalence estimates compared to actual patient number reported by participating centres

Abbreviations: DMSR = Danish Multiple Sclerosis Registry, ECTRIMS = European Committee for Treatment and Research, GMSR = German Multiple Sclerosis Registry, MS = multiple sclerosis, ICD-10 = International Classification of Diseases 10th edition

IV.2.f. Registry use

Centres from Austria, the Czech Republic and Denmark reported regular mandatory national registry use. The German reference centre reported mandatory registry use for centres participating in the German MS Association only. As a national registry with voluntary data entry was available in Poland, Romania and Slovakia, varying proportions of centres reported data entry, 20/24, 11/15 and 4/9 respectively. In Croatia, Hungary, Slovenia, and Serbia a national registry was not available, however, respectively 3/5, 7/29, 1/2 and 1/5 care units reported voluntary data entry into regional or international registries.

V. Discussion

V.1. Do Hungarian multiple sclerosis care units fulfil international criteria?

The standardization of MS care became a topic of conversation after diagnosis, imaging techniques, disease course classification and treatment of MS have changed substantially over the past few decades (McDonald WI et al., 2001, Polman CH et al., 2005, Polman CH et al., 2011, Thompson AJ et al., 2017, Rovira Á et al., 2015, Wattjes MP et al., 2021, Lublin FD et al., 2013, Ntranos A and Lublin F 2016, Lorscheider J et al., 2016, Rae-Grant A et al., 2018, Montalban X et al., 2018a, Montalban X et al. 2018b, Wiendl H et al., 2021). New discoveries regarding the underlying patomechanism of MS have been also integrated into diagnostic and therapeutic protocols to maintain the quality of life and working ability of individuals with MS (Kuhlmann T et al., 2023). Today, the clinicians' main goal should be to effectively treat MS, thus eliminating its impact on both quality of life and lifespan. The MS care unit guideline focuses on this aspect, and since its publication several papers have underlined the need for implementing these conditions in everyday clinical practise (Soelberg Sorensen P et al., 2019., Berger T et al., 2018, Berger T et al., 2020). Regarding the adaptation of the international recommendations, there was solely one initiative from Latin-America, where management of people with MS was pursued by general neurologist in general hospitals (Cristiano E et al., 2021). The panel of neurologists who reviewed the MSCU criteria reinforced the need for establishing specialized centres to diagnose and treat patients. However, they ratiocinated that demanding every facility to meet all aspect of these standards would be an unrealistic goal considering regional differences. With that said, to optimize MS care a realistic adaptation of international criteria was created, furthermore the panel also recommended the foundation of a reference system with close collaboration of specialized centres and General Neurology Departments. However, there was no study that examined the real-world operation of already existing MS centres. Thus, in our questionnaire-based national survey, we aimed to gain information on Hungarian MS centres' personnel and infrastructural equipment, DMT use and number of patients receiving care.

According to our results, seven care units fulfilled all aspect of minimum and recommended criteria, while further three facilities ensured minimum conditions only. This proportional distribution suggests that there is room for improvement for Hungarian MS centres. We also established those common insufficiencies, that might hinder patients in receiving equal quality care, thus facilitating future improvement of the proportion of missing criteria. While MS care units with more advanced background might be able to ameliorate current insufficiencies, for others, the international MS care unit recommendations may be too stringent to fulfil. In

Hungary, most commonly unfulfilled criteria were spasticity and pain specialist, neuro-ophthalmologist and oto-neurologist. Generally speaking, these specialties are rare to find, thus it would be reasonable to assign regional, fully equipped centres ensuring consultation for facilities with less fortunate background. On the other hand, considering that larger centres are usually more equipped, thus providing better care, it might be sensible to merge smaller units with greater facilities. Those seven centres, that lacked only secretary or MS nurse employment to fulfil minimum criteria, could apply for governmental funding of these employees, thus these shortcomings could be quickly ameliorated.

Even though, compared to other countries, in Hungary DMTs are funded by NHIF, regarding DMT use, we discovered that only half of the care units provided the entire spectrum of therapies (Moradi N et al., 2018, Claflin SB et al., 2022). Mainly highly effective infusions were not ensured, affecting equality in access to treatment. This phenomenon might be explained by the fact, that infusion therapies may pose a higher risk of serious adverse events, for example alemtuzumab-related cytokine storm or autoimmune disorders, ocrelizumab-associated infusion reaction or infection, and natalizumab-related progressive multifocal leukoencephalopathy (PML) or malignancies (Berger JR, 2006, Coles AJ et al., 2012, Montalban X et al., 2017). These severe side effects can only be accurately monitored and treated in centres with adequate equipment, emphasized by the ECTRIMS/EAN guideline as well (Montalban X et al., 2018a, Montalban X et al., 2018b). Our results further confirm the necessity of adaptation of the international guidelines. Further dissecting DMT use, we aspired to calculate the proportion of patients receiving DMTs. However, since 4 care units did not provide data on patient number, the whole Hungarian MS population could not be established, thus, we could not determine the proportion of people on DMTs. Regardless, we collected and analysed NHIF data, as the proportion of patients receiving low/moderately or highly effective DMTs can also be a measure of quality of care. According to our results, in Hungary 4 665 people received MS specific treatment in December 2020. We discovered that almost two-thirds of these patients used low/moderately effective injectable or oral treatment in equal proportions. Consequently, only one-third of patients received highly effective oral or infusion treatment in equal proportions. On one hand, the proportion of patients on low/moderately and highly effective treatment does not follow distribution of disease activity. According to the literature, approximately 40% of people have low/moderately active MS, while 60% of patients have highly active or aggressive phenotype (Comi G et al., 2017). Thus, comparing our data to international literature, almost one third of Hungarian patients might not receive adequate treatment (Simonsen CS et al., 2021, Spelman T et al., 2021, Magyari M et al., 2021, Hillert J

et al., 2021). On the other hand, the proportion of patients using low/moderately effective injectables is surprisingly high compared to those using low or moderately effective oral medications. Given that tablet therapies are less complicated to administer and do not carry the risk of local reactions, these proportions should be reversed. With that said, regarding the proportion of patients on highly effective oral medication was rather high compared to the proportion of individuals on highly effective infusion therapies. This proportion should also be reversed, as no evidence suggests, that tablets in the highly effective category have the same or higher effectivity as highly effective parenteral treatments (Thompson AJ et al., 2018). Proportion of low/moderately and highly effective treatment use also suggests, that in Hungary regarding therapeutic approach, escalation is preferred over induction. As the effective treatment window in MS is quite narrow, this approach might result in higher EDSS scores, development of psychopathological symptoms, and lower quality of life in the long run (He A et al., 2020). These factors have a negative effect on working capacity and might even lead to unemployment, increasing indirect costs of MS (Nicholas RS et al., 2020). Thus, even in the early stages of MS, adequately effective treatment options should be provided to prevent secondary progression. Even in the secondary progressive phase only highly effective DMTs are indicated, such as fingolimod, siponimod, natalizumab, ofatumumab, ocrelizumab and cladribine. In some rare instances use of interferon-β, with a weaker, B level evidence, can also be considered appropriate, however, other low/moderately effective medications display no evidence of effectivity in active-not progressive SPMS. In case of PPMS the only treatment option with proven effectivity and therapeutic indication is ocrelizumab.

The third, and also crucial objective of our study was to assess Hungarian patient number, as Hungary does not have a national MS registry. According to our data in 27 care units, 7 213 people receive regular medical care. Two centres did not participate in our survey, and two facilities did not fill out this part of the questionnaire. Even considering the absence of the aforementioned data, this proportion is representative, as it covers almost 90% of Hungarian MS centres, thus presumably 90% of the Hungarian MS population. Interestingly but not unexpectedly, actual patient number reported in our assessment falls far too short compared to calculated patient number according to prevalence estimates. To this date there are two recent prevalence estimates for comparison.

The epidemiological study conducted in Szeged, utilized rigorous, regional registry data of Csongrád-county, correspondent for 4% of the Hungarian population ensuring representativity (Biernacki T et al 2020, Bencsik K et al., 2017). According to this estimate, the standardized prevalence of MS in Hungary is 101.8/100 000, accounting for approximately 10 000 people.

Compared to the reported actual patient number, it still indicates an almost 2 500 people's worth of gap, which also underlines the importance of a national registry. In the other study, the 10th edition of the International Classification of Diseases (ICD-10) was used, resulting in a 130.8/100 000 prevalence, equalling approximately 13 000 patients (Iljicsov A et al., 2019). If this method can be considered reliable, then almost 6 000 people are not diagnosed or misdiagnosed, thus not receiving adequate medical care. However, considering that Hungarian ICD-10 system does not provide itemized settlements of accounts, the G35H0 code can signify several diseases causing demyelination of the CNS, thus this method could have overestimated actual prevalence. The use this method was previously also criticised by an American epidemiological study, underlying that ICD-10 codes are insufficient in providing detailed demographic and more specific healthcare data (Wallin MT et al., 2019). Furthermore, former international epidemiological studies using rigorous registry data also suggest, that national registries are those platforms that contain up-to-date, comprehensive, real-world data. Registry based studies provide information on not only diagnosis, but additional data as well, such as disease duration, used DMTs, therapeutic effectivity and so on, thus this method can be considered more reliable (Magyari M et al., 2021, Laakso SM et al., 2019, Hillert J and Stawiarz L, 2015, Steinemann N et al., 2018, Flachenecker P et al., 2008, Trojano M et al., 2008, Brola W et al., 2016).

Naturally, the remaining 4 care units, that did not participate, or did not provide information on patient number, to some extent could be responsible for this difference. However, other factors might also play a role in this phenomenon. People with slight neurological symptoms e.g. paraesthesia etc., might not seek professional help, and even those who receive medical attention might not get an accurate diagnosis of CIS or RRMS at disease onset, because of the improper application of latest diagnostic guidelines (Solomon AJ et al., 2021a, Solomon AJ et al., 2021b). Also, accurately diagnosed persons with moderate disease activity, might not regularly attend follow-up visits, because of the lack of insight into future consequences. Nevertheless, when discussing the challenges of diagnostics, the difficulties of diagnosing the progressive disease course should be emphasised. As persons with PPMS initially develop lower limb function involvement, e.g. paraesthesia, paraparesis, patients usually seek help from a general practitioner. GPs usually recommend consultation with rheumatologists, orthopaedics, or neurosurgeons. Patients due to their age, get often misdiagnosed with disc hernia, or other rheumatoid or orthopaedic disorder, delaying accurate diagnosis and adequate treatment by years (Cottrell DA et al., 1999). For a long time, there was no therapeutic option for people with PPMS. However, in 2018 ocrelizumab was accepted by the National Institute

of Health and Nutrition, therefore timely diagnosis and treatment of these individuals should be prioritized, as it can only be prescribed for patients having an EDSS below 5.5 points (Montalban X et al., 2017). At the same time, PPMS and SPMS patients with more advanced disease might slowly withdraw from attending follow-up visits, which might also contribute to the discovered gap. This phenomenon could be explained by either immobility due to greater disability or by the lack of adequate symptomatic treatment. Nonetheless, our result underline, that symptomatic treatment of these patients, such as spasticity, incontinence and chronic pain, should not be disregarded. Thus, in order to provide equality of access to treatment, the availability of spasticity and pain specialists should be ensured, which can be facilitated by appropriate training of MS specialist and MS nurses, stated in the international recommendation (Soelberg Soerensen P et al., 2019).

During our assessment we were the first to provide novel, representative data on real-world operation of MS centres revealing key insufficiencies suggesting possible solutions to amend quality of care. However, because of the nature of our study, reporting bias could have influenced our results, furthermore we only focused on national circumstances, with the intention of future extension. Moreover, patient reported outcome measures regarding quality of care were not included, thus patients' satisfaction with care was not determined, which also might be an interesting aspect for future studies.

Since the publication of our paper, there were a few studies examining similar aspects to ours in already existing centres or centre systems on a national level. An Italian article investigated whether different characteristics of care units have an effect on MS phenotypes (Bergamaschi R et al., 2022). In the national registry and Barometer of MS based investigation 106/166 centres participated representing all five regions of Italy. According to their results care unit characteristics did not significantly influence disease phenotype, nevertheless, substantial regional differences were discovered. Care unit density of the southern regions was lower, leading to a higher patient-to-care unit ratio and a greater deprivation index. Moreover, because of different DMT reimbursement policies 50% of centres reported difficulty in the access of treatments, thus resulting in inequalities in the quality of care, underlining the importance of providing standardized, multidisciplinary MS care. In a recent Belgian survey availability of multidisciplinary teams (MDT) and MS nurses and their association with quality of MS care was investigated (Van Hijfte L et al., 2024). In the study three separate questionnaires were used (collectively 916 patients, 22 MS nurses and 62 MS specialists reported data), thus viewpoints of all core members of everyday clinical practice were represented. Of the participating patients 65% reported access to an MDT, while 60% had access to MS nurses. Patients receiving care

from an MDT or an MS nurse were associated with more frequent symptomatic bladder treatment, physiotherapy and DMT use, spasticity and gait treatment respectively. Patients without access to MDT or MS nurses reported a need for these services. MS nurses were mainly employed by universities and some general hospitals, and received local non-governmental budget funding, while less than 10% of nurses received national health care insurance system funding, explaining the scarcity in availability. MS nurses were responsible for following 100-300 patients, providing psychosocial support, and performing physical and cognitive test batteries. MS neurologist who had access to MS nurses or MDTs had more patients and spent more time with each patient during follow-up visits, also emphasizing the need for standardized multidisciplinary care. Another regional study from Alberta (Canadian province, with over 4 million inhabitants) used Alberta Health Care Insurance Plan data and the G35H0 ICD-code to examine differences in health-care utilization in urban and rural areas (Balcom EF et al., 2024). According to their results, even though most Canadian provinces ensure government-funded tertiary MS care units with government-funded access to DMTs, only people living in urban areas had access to a centre within a 60-mile radius. People living in rural areas were constrained to travel long distances to get adequate care. As a result, people in these areas tended to visit near-by general neurologists or emergency rooms, where DMT prescription was not government-funded. This inequality was also represented by DMT use, as only one third of patients received any DMT. Of these patients, only 25% used highly effective treatments, while the rest received low/moderately effective medications. These data further highlight the need for a well-developed, accessible, multidisciplinary MS centre system. In a recent review on the management of MS in individuals above the age of 55, it was also emphasized that multidisciplinary care of older MS patients is essential (Fernández Ó et al., 2024). As these individuals might present with several comorbidities and polypharmacy, collaboration with internal medicine specialists, dietitians, continence specialists, physiotherapist and pharmacologists are non-negotiable. With rising prevalence of dementia consultation with neuropsychologists and speech therapist should also be ensured.

V.2. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants

In the past three decades management of MS has changed significantly, thus the standardization of MS care became necessary. The first international guideline on this topic was created in 2019, with a suggestion of world-wide adaptation (Soelberg Sorensen P et al., 2019). To this day, only Latin American countries participated in this movement, and aside from our Hungarian assessment, so far, no real-world data have been collected on current MS care circumstances

(Cristiano E et al., 2020, Kokas Z et al., 2022). Therefore, we aimed to gain a comprehensive overview of a larger region's MS management.

In our questionnaire-based international survey we learned that MS care in DSNS member countries takes place in specialized care units. In each country, MS neurologists and MS nurses are responsible for the management of the patients. However, as expected by the diverse financial and health care backgrounds, notable differences were discovered between countries. Moreover, because of different institutional circumstances, within country differences were detected. Our results revealed similarities in the sense of fulfilled and missing criteria. Regarding minimum criteria, the availability of MS nurses, pharmacists, and dietitians was homogeneously ensured. Neuropsychologist availability showed slight heterogeneity. In the availability of administrators, speech therapists, pain, spasticity and continence specialists high heterogeneity was revealed. On one hand, administrator paucity might be easily solved by increasing governmental funding of human resources and hiring employees, as these professionals are essential in quick and accurate documentation or in registry data recording. On the other hand, it might be more difficult to ensure availability of speech therapists, pain, spasticity and continence specialist. Nonetheless, these specialties are crucial in the management of patients with progressive disease course. Even though, DMTs to treat active PPMS and SPMS are reimbursed in the participating DSNS countries, these medications cannot reverse already acquired spasticity or incontinence. Adequate symptomatic treatment of patients plays a significant role in quality of life, thus, the availability of these specialties is unquestionable. As proposed in the MSCU recommendation, with further education, MS specialists and MS nurses could provide the role of a pain, spasticity or incontinence specialists (Soelberg Sorensen SP et al., 2019). Thus, the development of appropriate training programs could be a proper solution to this problem. Concerning recommended criteria, neuroradiologist, laboratory, internal medicine specialist, psychiatry and neurorehabilitation availability was homogenously ensured. The availability of microbiology, electrophysiology, ophthalmology, surgeon, neurosurgeon, and obstetrician-gynaecologist was slightly heterogenous. However, high heterogeneity was detected in the availability of a neuro-ophthalmologist and an oto-neurologist. To concur this issue, the foundation of a referral centre network should be considered. If a close collaboration between averagely and highly specialised MS centres could be achieved, consultation with more rare specialties could be ensured. This approach was already implemented by the establishment of the Danish, German, Austrian and Czech centre systems (Magyari M et al., 2021, Ohle LM et al., 2021, https://www.oegn.at/wp-content/uploads/2015/07/%C3%96GN_Kriterien_MSZentrum_18Februar2014.pdf,

https://www.czech-neuro.cz/content/uploads/2020/04/rs_odborna-2.0_final_pub_web-2.pdf, https://www.dmsg.de/service/kliniken-und-praxen/dmsg-ausgezeichnete-zentren). In these countries, a panel of professionals hand in hand with Ministry of Health Institutes (MoHI) and NHIFs, determined conditions concerning the personnel and instrumental background of an MS centre. To achieve centre qualification, a facility should prove the fulfilment of these conditions. Furthermore, institutes undergo regular quality control to renew centre status, in Denmark and Germany, the basis of this quality control is the national registry. Moreover, professionals also participate in regular training to remain up to date in the field. The system enables close collaboration between averagely and well-equipped centres, thus equality is ensured. Patient follow-up visits usually occur among ambulatory settings, yet inpatient care is provided if necessary. With these meticulous measures proper circumstances to diagnose and treat MS according to latest guidelines are ensured, thus these approaches are of great example for other countries.

When it comes to the quality of care and equality in access to care, besides personnel and instrumental background of centres, availability and reimbursement of DMTs play an important role. According to our survey, in participating countries all DMTs were funded by National Health Insurances (https://emsp.org/wp-content/uploads/2021/03/MS-Barometer2020-Final-Full-Report-Web.pdf). Accordingly, in 6/9 nations, most centres ensured the entire therapeutic arsenal. Nonetheless, a larger proportion of Hungarian, Polish and Romanian care units did not provide every available DMT. Only half of the Hungarian centres ensured all DMTs. This phenomenon can be attributed to the fact, that only one-third of care units fulfilled at least minimum criteria, thus providing appropriate instrumental and personnel background to safely use highly effective DMTs (Kokas et al., 2022). In Romania, besides less advanced equipment of centres, dimethyl-fumarate and alemtuzumab were rarely used because of limited experience with these treatments. Furthermore, cladribine was not available since it was not yet accepted by the Romanian National Agency of Medicines and Medical Devices (https://emsp.org/wp-content/uploads/2021/03/MS-Barometer2020-Final-Full-Report-Web.pdf). Solely two-thirds of Polish centres provided the entire spectrum of DMTs, in the rest only low/moderately effective DMTs were ensured. The reason behind this phenomenon is, when it comes to reimbursement of DMTs the Polish Health Care System distinguishes between general and specialized MS centres. While general MS centres only receive funding for low/moderately effective treatments, specialized MS care units can access all therapeutic options with reimbursement. Moreover, therapeutic escalation is strictly regulated, which might restrict highly effective DMT use (Brola W et al., 2015, Kapica-Topczewska K et al., 2020).

Nevertheless, even though DMTs are reimbursed in participating countries, there are still some inequalities when it comes to access to treatment, which can be attributed to less advanced equipment of centres. Thus, to provide better care, personnel and instrumental background of less advanced care units should be improved.

Aside from achieving close collaboration of MS specialists, NHIFs and MoHIs, another important aspect of improving quality of care, lies in regular quality control. Quality control assures that these authorities witness a "return on investment". Id Est, even though DMTs have high costs, with adequate treatment, indirect costs of MS decrease significantly on the long run, resulting in a better financial outcome. To make quality control possible, we should be familiar with certain quality indicators: patient number, disease course, disease activity, therapeutic adherence, and therapeutic efficacy. These data could be extracted from national registries (Magyari M et al., 2021). One of the most important quality indicators is actual patient number. In our assessment, we found that reported patient number was only comparable to calculated patient number according to prevalence estimates, if a national, regularly refreshed registry was available. For example, in Austria and the Czech Republic where mandatory registry use was required, actual patient number well represented estimated patient number (Salhofer-Polanyi S et al., 2017, https://nfimpuls.cz/images/docs/remus_zaverecne-zpravy/aj_zaverecna_zprava_2020_12_souhrnna_web.pdf). The Croatian, Polish and Romanian voluntary-used registries provided somewhat comparable results (Benjak T et al., 2018, Kapica-Topczewska et al., 2018, Cornea A et al., 2015). In the rest of the countries, where only regional registries were present, or some care units voluntarily participated in data entry into regional or international registries, results were not commensurable at all (Kokas et al., 2022). Moreover, in several countries, because of a lack of a well-maintained registry only outdated prevalence data were available (Peterlin B et al., 2006). Thus, our results and the fact that these databases can be a basis for quality control also support the need for well-maintained national registries.

With this survey, we first provided a comprehensive overview on real-world MS management of Central-Eastern European countries. We identified several shortcomings of current MS care, and showed already existing, well-working examples how to bridge certain gaps and how to ensure equality in access to care with a reliable quality control system. Nonetheless, self-report questionnaires might pose a risk of report bias.

Following the release of our study, on this topic several articles have been published with different designs. A review from Africa has highlighted the fact, that while in developed countries it is a realistic aim to establish multidisciplinary MS care units to amend MS care, however, in less privileged countries, having more and better-equipped hospitals and access to

general neurologists at all (not specialized in any field) is a more pressing issue (Aderinto N et al., 2023). Not to mention access and funding of more treatment options should also be improved, as in most of these countries only a fragment of the therapeutic arsenal was available in a non-government-reimbursed fashion. Moreover, education on MS was also insufficient not only among the general public, but within the medical community as well, thus improvements in this area should be likewise prioritized. With that said, not only developing countries lack in the field of MS care, as in some developed countries, there is much room for improvement. For example, Canadians conducted a survey on MS care among health care providers (HCPs) working in MS clinics, using a questionnaire with open-ended questions (Petrin J et al., 2023). In this survey 85 HCPs participated from 20/34 MS clinics. According to the results, HCPs deemed MS neurologist, MS nurses, physiotherapists, occupational therapists, mental health providers, neuroradiologists, neuro-ophthalmologists and urologists necessary in providing adequate MS care. Moreover, a need for personnel responsible for clinical assessments and data recording was also highlighted. They also emphasized the importance of working in a single clinic instead of separate units as a more time and energy saving measure for both patients and HCPs. Thus, the importance of establishing Sorensen-type MS care units was confirmed again. In this study it was also mentioned, that even though every inhabitant had a health insurance, not all medical interventions or therapies were funded, thus improvements in this area should be implemented as well. A recent study from the United States of America (USA) examined access to MS neurologists and MS centres across the USA using Medicare data with a cross-sectional design (McGinley MP et al., 2024). They identified 185 MS centres and over 15 000 MS neurologists, revealing a patient to centre ratio of 3 500 – 4 000. Furthermore, regional differences in access to care between urban and rural areas, and ethnic inequalities were also observed. Moreover, it was revealed that uninsured or disabled individuals in general lacked access to care. According to this study, in most rural areas general neurologists provided care for pwMS, who could refer them to specialized MS centres. To improve access to care authors proposed the need for more outpatient care units and teleconsultation as a solution. Thus, even in large, developed countries, such as Canada or the USA, MS personnel and multidisciplinary management of MS might be insufficient, henceforward improving the quality of MS care remains a global goal of the 21st century.

VI. Conclusion

VI.1. Do Hungarian multiple sclerosis care units fulfil international criteria?

Our work is the first to provide data on the operation of an already existing MS care unit system according to the international recommendation. Our survey suggests, that in order to provide equality in access to treatment, and to ensure adequate care for people with MS, over half of the Hungarian MS centres should improve personnel circumstances and DMT availability. With a well-developed centre system and elaborate patient pathways, where general practitioners and other specialities are thoroughly educated, even the diagnosis of PPMS might become accelerated. With timely diagnosis and appropriate symptomatic treatment of individuals with progressive disease, actual patient number receiving care in centres might correspond to estimated patient number. To properly keep track of patients, a national registry is still indispensable. With that said, this study, supported by real-world data, is the first to reveal that without an adequate centre network and stringent quality control, 25% of patients cannot obtain access to adequate care. Moreover, even one-third of patients who were able to access MS specific medical care, don't receive therapy according to their disease activity, thus leading to progression and irreversible impairments, decreased working ability and quality of life.

VI.2. Real-world operation of multiple sclerosis centres in Central-Eastern European countries covering 107 million inhabitants

Our study is the first and most comprehensive international assessment, covering the largest region and greatest proportion of inhabitants regarding the real-world operation of existing MS care units to date. Our results reinforce the need for adaptation of the international MS care unit criteria considering economic and health care differences among countries. To provide adequate care for people with MS, personnel and instrumental background, as well as DMT reimbursement should be ensured. Our results highlight that less than half of the surveyed Central-Eastern European countries provide homogenous availability of multidisciplinary care for people with MS, while in the rest of the nations, institutional and personnel background to provide adequate care is heterogenous. Developing a centre system, similar to the Austrian and Czech examples, where institutions with less fortunate background closely collaborate with more developed centres, enabling consultation with the rarest specialties, might amend MS management. This Central-Eastern example and the Danish and German systems detailed above might be a valuable guide for countries with heterogenous institutional and personnel background to follow. Furthermore, our study also confirms, that in order to sufficiently improve MS care, MS specialists, Health Insurance Funds and Ministry of Health Institute should closely cooperate, and regular, registry-based quality control should be ensured.

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IX. Appendix