Socio-economic analysis:

The impact of multiple sclerosis in Romania

Contents

1 Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic (hormone)
NHIH	National Health Insurance House
NHPP	National House of Public Pensions
ICS	Isolated Clinical Syndrome
DIS	Dissemination in space
DIT	Dissemination in time
EDSS	Expanded Disability Status Scale
IHME	The Institute for Health Metrics andEvaluation
NIPH	National Institute of Public Health
MRI	Magnetic Resonance Imaging
CSF	Cerebrospinal fluid
MH	Ministry of Health
CNS	Central Nervous System
WHO	World Health Organization
NMR	Nuclear Magnetic Resonance
MS	Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
CNS	Central Nervous System
YLD	Years Lost due to Disability
YLL	Years of Life Lost

2 Executive summary

Purpose and scope

This study examines the effects of multiple sclerosis in Romania by estimating and analysing the economic and social impact on patients, families, the state budget, as well as on society, in general. The reference year of the study is 2016. The limited number of scientific articles exploring this pathology at national level has led to the idea of developing a primary assessment with information resources available, at the health system level, for a complex issue - management of multiple sclerosis in Romania.

This exercise is a first initiative to fill in the important information gap about this disease. The ultimate goal of this material is to support the development of evidence-based health policies aimed at improving the quality of the services provided and their focus on patients.

This study was conducted by EY Romania at the request of Roche Romania.

The structure of the study is built around specific objectives and includes an overview of the disease and its epidemiology (disease prevalence and incidence, patient profile), identification and illustration of patient pathway (including available therapeutic options, as well as the potential access and barriers to treatment), the estimation of direct and indirect costs of the disease, as well as the estimation of multiple sclerosis patients progression over the time between 2018-2028.

Methodological considerations

In order to meet the objectives of the study, the methodological approach used was aimed at:

- Overview on ***multiple sclerosis*** – built around information extracted from scientific literature.
- ***Disease epidemiology*** – after a systematic review of the literature, data on the multiple sclerosis epidemiology in Romania were found to be limited (existing studies provide contradictory values for the indicators, or are very old and do not provide geographical coverage at national level). Therefore, due to the aforementioned facts and to consultation with stakeholders in this therapeutic area, the prevalence of the disease was estimated based on access and usage of services. The disease incidence was extracted from a recent response from the Ministry of Health submitted after parliamentary interpellation.
- Information related to the ***patient pathway*** and the available treatment methods were obtained and synthesized by consulting the Romanian therapeutic protocol for the treatment of multiple sclerosis and scientific literature. In order to collect information on patients' access and the potential treatment barriers they encounter, an online quality questionnaire addressed to patients diagnosed with multiple sclerosis was used, by means of organizations in this area.
- The estimation of ***direct costs*** used a bottom-up approach, based on the clinical guidelines for the diagnosis and treatment of the disease. For example, the cost components for patient diagnosis have been compiled from the latest diagnostic and treatment guide in neurology (Băjenaru, 2010). The exceptions to this methodological calculation approach are estimates of hospital care costs for which data from national records and transport costs were used, estimated based on an approximation of the distance between the patient's residence and the closest hospital.

- The estimation of ***indirect costs*** was performed based on a mixed approach. Productivity lost due to mortality and disability was calculated using a disease burden measurement indicator, then used as a multiplier for GDP per active population for the reference year. For the purposes of estimating the indirect costs of disability pensions, disability allowances and medical leaves, a bottom-up approach was used based on the prevalence and demographic profiles of patients in the reference year of the study, and the responses received as a result of the qualitative questionnaire submissions.

The components of the direct and indirect costs for which estimates were provided in the study are:

- **Direct costs:**
- Costs with disease diagnosis and monitoring
  - Costs with drug treatment
  - Costs with clinical and paraclinical services
  - Costs with the hospitalisation of patients
  - Costs generated by comorbidities associated with the disease
- **Indirect costs:**
  - Lack of productivity due to disability
  - Lack of productivity due to premature death
  - Disability pensions
  - Disability allowances
  - Sick leaves
  - Patient transport

Results of socio-economic analysis

According to the Romanian therapeutic protocol for the treatment of multiple sclerosis, multiple sclerosis is the most disabling disease of the young adult, affecting over 7,500 patients in 2016. Of these, about 5,000 had access to the public health system in 2016, with active disease. The estimated level of access to diagnosis and treatment in line with therapeutic protocols reported by patients with multiple sclerosis in Romania is 64%. Approximately 75-80% of patients initially have a relapsing form of the disease. This condition has important socio-economic implications and generates severe deterioration in the quality of patients' lives. The results of this study indicate a number of inefficiencies in the patients' pathway and access within the health system in Romania.

Firstly, clinical and paraclinical services provided in the public health system do not cover the needs of the entire population suffering from this disease, with only 6 cities being included in the national multiple sclerosis treatment program, at national level. In terms of drug treatment, the most important limitations arise as a result of such access problems. Moreover, the procedures for assessing and marketing drugs in Romania, although under on-going reform, generate significant gaps between the emergence of innovative drugs and when the drugs start being used by patients. All these problems generate additional costs, covered by patients: transport costs (most people are not in close proximity of treatment centres), costs for symptomatic treatment, costs for treatment of side effects or comorbidities, other costs for patient orientation towards the private environment especially for rapid diagnosis (MRI).

Scientific literature highlights a reduction in the life span of people diagnosed with multiple sclerosis ranging from 6-13 years to the life of a healthy person. In the absence of specific data from our country and taking into account World Bank data on the average life expectancy at birth in Romania for the reference year of the study, and the validations of the medical experts consulted, this study takes into account an **average decrease of 9.5 years**, namely a **life expectancy of 65.5 years** for patients diagnosed with multiple sclerosis in Romania, compared to 75 years, the life expectancy of a healthy person.

The results of the analysis indicated that multiple sclerosis in Romania is a rare disease with an **annual prevalence of 38.3** cases for every 100,000 inhabitants, an **annual incidence of 4.9** cases every 100,000 inhabitants and as **annual rate of mortality of 0.33** deaths for every 100,000 inhabitants. These values are approximations for the reference year of the study.

The total cost of multiple sclerosis in Romania, according to the results of this study, is **RON 412.5 million (EUR 91 million)** per year, calculated for the reference period of the study (2016). They can be classified into **direct costs - RON 272 million (EUR 60 million)** and **indirect cost - RON 140,5 million (EUR 31 million)**. For the reference year 2016, the total number of years lost due to disability in multiple sclerosis patients in Romania is **2,595**, with an indirect productivity cost of approximately RON 100 million (EUR 22 million). The total number of patients for whom these costs were calculated varies according to their differences in access to medical services or treatment for direct costs or by occupancy, disability, severity of their disease in indirect costs.

Therefore, in 2016, the total costs per patient have registered **RON 85,500 (EUR 19,000)**, of which **RON 56,500 (EUR 12,500)** direct costs and **RON 29,000 (EUR 6,500)** indirect costs.

Main findings

According to the results of the analyses carried out within this study, **66% of the total costs** of multiple sclerosis in Romania, in 2016, **are due to the direct costs** for diagnosis, treatment and monitoring this disease, while **34% of the total costs of the disease are indirect costs.** This share is based on the qualitative findings obtained during the course of the study, from the answers provided in the questionnaire administered to the Romanian patients diagnosed with multiple sclerosis, but also from the validations of the medical experts consulted, which reveals that in Romania, nowadays, most of the medical services are delivered directly in the hospital.

The services supplied through the national multiple sclerosis program amount to **5.7% of the budget for high-risk chronic diseases,** from the national curative programs reported by NHIH in the reference year of the study.

The profile of the Romanian patient with multiple sclerosis was outlined based on the responses to an online questionnaire administered in the study, highlights that the Romanian patient with multiple sclerosis:

- mean age of 37 years;
- female - only about 30% of patients are men in Romania;
- regularly active on the labour market;
- was diagnosed with multiple sclerosis about 5 to 10 years ago;
- the diagnosis of multiple sclerosis has had a negative impact on the patient's life;
- is currently undergoing immunomodulatory treatment.

The main disease-related barriers reported by patients are social stigma associated with this disease, the frequent lack of medication on the market in Romania, the lack of interest in patients from medical staff, limited access of patients to information, increasing difficulties to access drugs, lack of communication between physicians and patients and concerns related to access to the health system.

Managing the burden of multiple sclerosis in Romania

- Improving the quality of healthcare and health for every individual suffering from multiple sclerosis;
- Generating solid evidence (disease registers) to motivate decisions and adapting public health policies to improve patients' quality of life.

3 Health concern

3.1 Overview on multiple sclerosis

In 1868, the researcher Jean-Martin Charcot discovered multiple sclerosis. Multiple Sclerosis (MS) is a chronic inflammatory demeyelination disease of the Central Nervous System (CNS), which affects young adults and, over subsequent decades, it may turn into a progressive neurodegenerative disorder associated with major clinical disabilities. Multiple sclerosis is the most disabling disease of the young adult. The disease is likely to occur as a result of a complex combination of genetic factors, environmental triggers and infectious events. It is believed that MS lesions originate from an autoimmune disease where the immune system recognizes CNS myelin as a foreign body and, as a result, activates itself to destroy it. This process leads to the formation of demyelinated plaques, which are subjected to axonal damage and neurodegeneration, at some point[1]. However, the causes of the disease are unknown.

The International Federation of Multiple Sclerosis has a number of key issues[2] with regard to multiple sclerosis:

- It is a progressive disease of the central nervous system, for which there is no remedy.
- More women than men have MS, the ratio being of three to two.
- It is the most common central nervous system disease in young adults.
- It is not directly hereditary, although genetic predisposition plays a role in its development.
- It is not contagious or infectious.
- Diagnosis generally occurs between the age of 20 and 40 years, although the disease may be triggered earlier.
- It has a wide range of symptoms, fatigue being the most common.
- The MS incidence increases in countries located further from the Equator.
- There are currently treatments that can alter the course of the disease.
- Many of the MS symptoms can be managed and treated successfully.

3.1.1 Types of disease

Multiple sclerosis has several classifications depending on clinical evolution or severity. The most recent classifications present in the literature refer to these subtypes in **relapsing-remitting** and **primary progressive forms**. These two large groups can evolve over time in several subtypes[3]. For the accuracy of this study, the national classification standard proposed by the Romanian Journal of Neurology was used by the Diagnostic and Treatment Guide for Multiple Sclerosis[4]:

Relapsing-remitting form (RRMS)

The relapsing-remitting form (RRMS) of the disease is characterized by definite clinical outbreaks with complete or incomplete clinical recovery (with sequelae). Some outbreaks may have no clinical recovery at all. Between outbreaks, neurologic deficits are due to accumulation of sequelae, without clinical progression. The relapsing-remitting form of MS (RRMS) is the most common clinical form (60-70% of cases) - it occurs more frequently in women and starts most often around the age of 30 years.

[1] Julia SCHAEFFER, Chiara COSSETTI, Giulia MALLUCCI, Stefano PLUCHINO, Department of Clinical Neurosciences, University of Cambridge, UK, Scleroza Multiplă, in Neurobiology of Brain Disorders, Biological Basis of Neurological and Psychiatric Disorders, 2015, pages 497-520.
[2] Multiple Sclerosis International Federation, https://www.msif.org/.
[3] G MATHEY, M MICHAUD, S PITTION-VOUYOVITCH, M DEBOUVERIE, Classification and diagnostic criteria for demyelinating diseases of the central nervous system: Where do we stand today?, in Rev Neurol (Paris), Apr 2018
[4] O. BĂJENARU, C.D. Popescu, C. Tiu, D. Marinescu, Gh. Iana, Diagnosis and Treatment Guide for Multiple Sclerosis, in the Romanian Journal of Neurology, Aug 2008.

Secondary progressive form (SPMS)

The secondary progressive form (SPMS) is characterized by partial recovery after outbreaks and continuous progression, interrupted or not by outbreaks, occasionally with plateau phases. This form is the transformation of the relapsing-remitting type, after an average of 10 years of disease evolution. Some features of RRMS can identify the increased risk of some patients progressing to a form of SPMS: older age at onset (over 35 years), more than two relapses in the first year, increased frequency of relapses in recent years of evolution of the disease.

Primary progressive multiple sclerosis (PPMS)

The primary progressive multiple sclerosis (PPMS) is characterized by continuous progression from onset, occasionally with plateau phases and minor, temporary improvements. This form has a relatively equal distribution between the sexes; it starts around the age of 40 and affects the spine more frequently and more severely, from the onset.

Progressive Relapsing form (PRMS)

This form of disease is characterized by continuous progression from onset, but with acute clinical worsening episodes with or without full recovery. It is, in fact, a particular form in which the primary progressive, but therapeutically important, form may evolve.

Depending on the clinical severity, it is also described as particular forms of MS, **malignant variant** (fast progressive form, with severe disability or death, relatively soon after onset) and **a benign variant** (mostly a clinical assessment, than an actual clinical form, diagnosed whenever there is no clinical worsening, 10 years after onset, or when the EDSS score of 3 has not been exceeded).

After establishing the positive diagnosis of multiple sclerosis and its evolutionary form, it is now mandatory for any neurologist to assess the degree of patient disability according to the EDSS score (Kurtzke Expanded Disability Status Scale). This assessment is necessary both for assessing the evolutionary prognosis of the patient, but at least equally, it is an important criterion in establishing an optimal therapeutic conduct.

3.1.2 Causes and manifestations of the disease

The mechanism[5] responsible for MS may be synthesized for two reasons:

- (1) the immune system has destroyed the myelin sheath, and
- (2) the inability of myelin-producing cells to produce new blots.

Although the cause of multiple sclerosis is unknown, it is believed that the variation in gene doses[6] plays a role in the risk of developing the disease. Changes in the HLA-DRB1 gene are the most potent genetic risk factors for developing multiple sclerosis. Other factors associated with an increased risk of developing the disease include changes in the IL7R gene. Although it is believed that MS is not a hereditary disease, the risk of multiple sclerosis is higher for people who have or had relatives with MS than in the general population[7].

In addition, various environmental factors - infectious and non-infectious - have been proposed as risk factors for multiple sclerosis[8]:

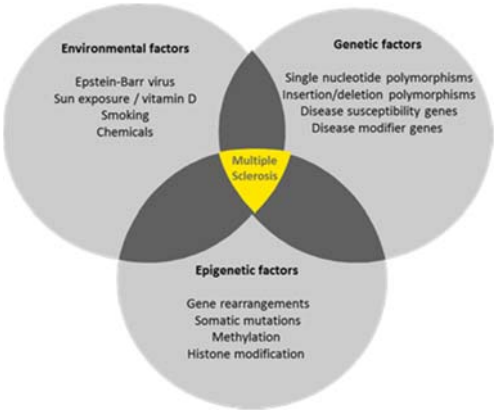
- **microbial infection** – microbial infection has been associated with the main processes of introducing and increasing the incidence of MS;
- **viral infection** – three pieces of evidence support viral infection in MS: (1) the presence of oligoclonal bands in the central nervous system fluid of MS patients; (2) many viruses related to human demeyelination encephalomyelitis; (3) viral infections also induced demyelination in animals. The lymphocytic choriomeningitis virus is the virus responsible for MS symptoms;

[5] Khaled M. M. KORIEM, Multiple Sclerosis: New insights and trends, in Asian Pacific Journal of Tropical Bioledicine, Volume 6, Issue 5, May 2016, paginile 429-440.
[6] U.S. National Library of Medicine. Genetics Home Reference. Multiple Sclerosis.
[7] Multiple Sclerosis International Federation, https://www.msif.org/.
[8] Alberto ASCHERIO, Kassandra L. MUNGER, Environmental risk factors for multiple sclerosis. Part I: the role of infection, in Annals of Neurology, April 2007.

- **other infections** – MS can also be induced by smoking, stress, and environmental toxins (especially exposure to solvents). The contaminated diet and hormonal intake may be associated with MS.

The development of multiple sclerosis is based on complex interactions between genetic and environmental factors.

Figure 1: Multiple Sclerosis – Etiological Factors [9]



Symptoms of multiple sclerosis can be classified into primary, secondary or tertiary symptoms[10].

- **Primary:** weakness, sensory loss and ataxia (inability to coordinate muscular movements) - directly related to demyelination and axonal loss.
- **Secondary:** urinary tract infections due to urinary retention - the result of primary symptoms.
- **Tertiary:** reactive depression or social isolation - the result of the social and psychological consequences of the disease**.**

Depending on their frequency, these symptoms can also be divided into:

- **Frequent**: fatigue and weakness; decrease in balance; spasticity and gait problems; depression and cognitive problems, urinary, digestive and sexual dysfunction problems; sensory loss and neuropathic pain.
- **Less frequent:** dysarthria and dysphagia, vertigo and tremor.
- **Rare:** seizures, hearing loss and paralysis.

3.2 Exacerbations and complications of the disease

A key component of multiple sclerosis is the emergence of clinical worsening episodes with either new symptoms or aggravation of older symptoms within a few days or weeks. These are known as exacerbations of multiple sclerosis. Exacerbations have been typically defined[11] as episodes of focal neurological disturbances lasting more than 24 hours without a known explanation and preceded by a period of clinical stability lasting at least 30 days. Symptoms fluctuation or aggravation, accompanied by fever or infection, are considered as medical exacerbations only if they meet the above criteria. These are often called pseudo-exacerbations. Approximately 80% of patients with MS show, in an initial stage, the (relapsing) remitting form of the disease[12]. as episodes of focal neurological disturbances lasting more than 24 hours without a known explanation and preceded by a period of clinical stability lasting at least 30 days. Symptoms fluctuation or aggravation, accompanied by fever or infection, are considered as medical exacerbations only if they meet the above criteria. These are often called pseudo-exacerbations. Approximately 80% of patients with MS show, in an initial stage, the (relapsing) remitting form of the disease they appear, was aimed at shortening the duration of the attacks and obtaining a full recovery. This procedure is commonly performed with anti-inflammatory agents, such as steroids and ACTH.

[9] Jafari NAGHMEH, Risk factors in cause and course of multiple sclerosis, Stichting MS research, page 16.
[10] Aliza BEN-ZACHARIA, Therapeutics for multiple sclerosis symptoms, in The Mount Sinai journal of medicine, New York, 2011.
[11] Daniel ONTANEDA, Alex D. RAE-GRANT, Management of acute exacerbations in multiple sclerosis, in Annals of Indian Academy of Neurology, 2009.
[12] Idem.

The complications associated with multiple sclerosis include: fatigue, loss of mobility and spasticity, pain, bowel dysfunction, sexual dysfunction, urinary emergency, nocturia, urinary incontinence, visual problems, difficulty in swallowing, speech and hearing difficulties, pulmonary problems, osteoporosis, cognitive problems, depression.

3.3 Diagnosis stages and severity levels

The diagnosis of multiple sclerosis is based on neurological symptoms and signs, alongside evidence of CNS lesions in space and time. The NMR is usually sufficient to confirm the diagnosis, when specific lesions accompany a typical clinical syndrome but, in some patients, additional medical investigations are required, by examining the cerebrospinal fluid and by conducting neuropsychological tests[13].

The differential diagnosis includes many conditions and varies according to the clinical presentation. The differential diagnosis dictates what medical investigations might be required[14]. A detailed general medical examination, as well as a complete neurological examination, is essential because an initial clinical finding through a neurological examination remains a prerequisite for diagnosis. Patient history may reveal previous symptoms suggestive of MS, such as unilateral loss of vision, blurred or double vision, Lhermitte's sign, or motor or sensory disorders. These symptoms are useful for diagnosing MS.

Once the clinical examination has revealed evidence of an MS attack, the usual next step is a brain scan by MRI. If the patient experiences changes in the spinal cord examination, suggesting MS, then both a brain NMR and a spine NMR should be performed.

However, differential diagnosis should also be considered, since diseases such as viral encephalitis, syphilis, subacute sclerosing panencephalitis and disseminated acute encephalomyelitis may also produce CSF abnormalities. These paraclinical findings, although very suggestive of MS diagnosis, they are not always specific to it, and it is relevant to reiterate that the diagnosis of MS remains primarily a clinical one and that the differential diagnosis should always be considered.

Below are some diagnostic features[15] of the four forms of multiple sclerosis:

- Multiple sclerosis, relapsing-remitting form (RRMS): The McDonald Diagnostic Criteria indicate the need for objective clinical indications, both clinical or radiological or with alleged potential to demonstrate the presence of dissemination in space and time, when the diagnosis of RRMS is stated. RRMS is characterized by recurrent seizures or relapses that vary in frequency and severity, but there is a stable period between relapses. However, a patient who has relapsed cannot fully return to normal, and many patients remain with residual defects.
- Multiple sclerosis, secondary progressive form (SPMS): SPMS is characterized by at least one relapse followed by the progressive worsening of the medical condition. This progression may develop slowly after an initially isolated clinical syndrome but, more commonly, it follows a well-defined RRMS. As a result, a well-diagnosed isolated clinical syndrome is the minimum criterion for determining this type of multiple sclerosis. Its development is progressive, but in some patients there may be periods of relative stability. During the progressive course of the disease there may be intermittent relapses.
- Multiple sclerosis, primary progressive form (PPMS): PPMS is a disease that progresses slowly from diagnosis, and from a medical point of view, most patients suffering from PPMS show the symptoms of progressive myelopathy or progressive cerebellar dysfunction. A final diagnosis may be difficult for many patients with this form of disease, but the poor use of McDonald's criteria could help avoid diagnostic errors.
- Multiple Sclerosis, progressive relapsing form (PRMS): PRMS includes patients who accumulate deficiencies over many years and remain very functional. Several studies indicate that this form of multiple sclerosis should probably only be diagnosed retrospectively.

New diagnostic and treatment guidelines also define the isolated clinical syndrome (ICS) as a form of multiple sclerosis. ICS is defined by a first neurological episode that lasts for at least 24 hours, having an inflammatory or demyelinating substrate, within the central nervous system. Patients with isolated clinical syndrome may develop clinically defined MS - most patients with ICS assessed by monthly NMR developed MS by fulfilling the McDonald criteria within 3 months after the initial assessment.

[13] Wallace J. B. FRACP, Todd A. HARDY, Franz FAZEKAS, David H. MILLER, Diagnosis of multiple sclerosis: progress and challenges, in The Lancet, Volume 389, Issue 10076, April 2017, pages 1336 – 1346.
[14] D. MILLER, A. COMPSTON, The differential diagnosis of multiple sclerosis, in McAlpine's Multiple Sclerosis, 4th ed., 2006, pages 389-437.
[15] Barrie J. HURWITZ, The diagnosis of multiple sclerosis and the clinical subtypes, in Ann Indian Acad Neurol 2009; 12, pages 226-230.

The McDonald diagnostic criteria for multiple sclerosis, last reviewed in 2017, are the currently recognized diagnostic criteria for multiple sclerosis. These are presented in Appendix 2 to this study.

Multiple sclerosis comprises of various forms with variable presentations, as shown in the table below. Progressive relapsing MS is a diagnosis involving the accelerated progression of MS during 5 years after diagnosis. Alternative evolutions of MS may include benign forms, the patients preserving the neurological function for 15 years after diagnosis. In the relapsing-remitting form of MS (RRMS), patients have recurrent outbreaks, but have a tendency to be stable between the outbreaks. These outbreaks may vary in terms of appearance and severity, but some patients develop permanent residual deficiencies. Secondary progressive MS is a sub-type of RRMS and it is characterized by low disabilities and a high functional status of the patients. In case of secondary progressive MS, gradual worsening occurs, in time, after at least one outbreak. This form of MS can occur after an isolated clinical syndrome; however, it may also occur in the RRMS. Finally, the primary progressive MS is a less common form, but steadily progressive, of MS. The highlighting feature of this form is progressive myelopathy or cerebellar dysfunction[16].

Table 1: Stages of Multiple Sclerosis Evolution [17]

Type	Patient's ratio Diagnosed at onset	Remission periods	Symptom Progression
Relapsing-Remitting MS (RRMS)	85%	Significant remission periods	Relapse periods
Secondary Progressive MS (SPMS	*RRMS left untreated,, 50% of patients will develop SPMS within one decade after the first diagnosis	Partial recoveries orr periods of remission	The disease does not disappear between cycles; instead it gets worse
Primary Progressive MS	10%	None	Occasional plateaus in their symptoms as well as minor improvements in function that tend to be temporary
Progressive Relapsing MS	5%	None	Steadily get worse

3.4 Life expectancy

Although the possibility of developing a severe, long-term disability, in multiple sclerosis, is not strictly a cause of death, statistically, MS patients have a high mortality compared to the rest of the population[18]. There are contradictory data on the relationship between gender and mortality in multiple sclerosis. Although many studies have found a longer life expectancy in female groups, others have reported no difference between men and women or even a higher risk of mortality in female patients. The lack of homogeneity could be partly attributed to changes in the ratio between female and male patients over time. The increased incidence of multiple sclerosis among women, observed in the last 4-5 decades; it was not obvious 3-4 generations ago, when the gender ratio was almost balanced. Recent studies have shown that the gender-related ratio in multiple sclerosis is still changing in many countries[19]. In Romania, according to the latest epidemiological studies, gender distribution is imbalanced, towards the female sex (about 70% of cases).

According to the World Bank, in Romania, the average life expectancy at birth for the reference year 2016 is 75 years. The differences in mortality rates between multiple sclerosis patients and the healthy population have an impact on the life expectancy. Literary studies indicate a reduction of 6-13 years relative to healthy population values[20] [21].

[16] Idem.
[17] Aysha KHAN, Nader TAVAKOLI, Richard G. STEFANACCI, Management of Medical Complications in a Long-Term Care Patient with Multiple Sclerosis, in Annals of Long-Term Care: Clinical Care and Aging.2017; 25(2), pages 44-47.
[18] Antonio SCALFARI, Volker KNAPPERTZ, Gary CUTTER, Douglas S. GOODIN, Raymond ASHTON, George C. EBERS, Mortality in patients with multiple sclerosis, in Neurology. The Official Journal of the American Academy of Neurology, July 2013, 81(2), page 184.
[19] Antonio SCALFARI, Volker KNAPPERTZ, Gary CUTTER, Douglas S. GOODIN, Raymond ASHTON, George C. EBERS, Mortality in patients with multiple sclerosis, in Neurology. The Official Journal of the American Academy of Neurology, July 2013, 81(2), page 187
[20] AD SADOVNICK, GC EBERS; RW WILSON, DW PATY, Life expectancy in patients attending multiple sclerosis clinics., in Neurology, 1992, Pages 991-994
[21] N KOCH-HENRIKSNE, H BRONNUM-HANSEN, E STENAGER, Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. in J Neurol Neurosurg Psychiatry, 1998, pages 56-59.

Given that there are no specific data for Romania, the approximate life expectancy for patients with multiple sclerosis in Romania can be calculated by deducting the average stated in the literature to reduce life expectancy (9.5 years):

65.5 years - 13% decrease compared to the healthy population. Given that there are no disease records, nor better data on the causes of death in Romania, these values are approximations.

3.5 Causes of mortality

Patients suffering from MS can die from causes that are not related to the disease itself. Nevertheless, on average, in more than half of the cases, MS is recognized as the cause of death in death certificates[22].

The table below shows the underlying causes of death of patients with multiple sclerosis, as shown by the scientific studies conducted over time.

Table 2: The main causes of death of patients suffering from multiple sclerosis [23]

	Phadke (1987)[24]	Sadovnick et al. (1991)[25]	Koch-Henriksen et al. (1998)[26]	Sumelahti et al. (2002)[27]	Bronnum-Hansen et al. (2004)[28]	Redelings et al. (2006)[29]	Grytten Torkildsen et al. (2008)[30]	Hirst et al. (2008)[31]	Smestad et al. (2009)[32]
No. of deaths	216	145	6.068	219	4.254	27.319	198	221	263
Causes of death, %									
MS	62,0	47,1	55,4	58,0	56,4	61,2	56,5	57,9	50,0
Cardio-vascular disease	19,0	20,6	17,6	26,0	15,5	10,9	13,1	16,0	14,4
Cancer	12,0	30,2	8,6	35,0	10,1	8,5	10,6	9,5	9,8
Resp. disease	3,2	//	5,1	//	4,7	19,7	5,1	47,5	1,5
Accident/ suicide	//	28,6	3,8	5,0	4,5	0,3	2,5	0,0	5,3
Other	2,7	//	9,5	//	13,5	//	6,6	8,6	//

[22] N KOCH-HENRIKSNE, H BRONNUM-HANSEN, E STENAGER, Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. in J Neurol Neurosurg Psychiatry, 1998, page 184
[23] Antonio SCALFARI, Volker KNAPPERTZ, Garry CUTTER, Douglas S.GOODIN, Raymond ASHTON, George C. EBERS, Mortality in patients with multiple sclerosis, in Neurology. The Official Journal of the American Academy of Neurology, July 2013, 81(2), page 184.
[24] JG PHADKE, Survival pattern and cause of death in patients with multiple sclerosis: results from an epidemiological survey in north east Scotland, in J Neurol Neurosurg Psychiatry, 1987; 50, pages 523-531.
[25] AD SADOVNICK, K EISEN, GC EBERS, DW PATY, Cause of death in patients attending multiple sclerosis clinics, in Neurology, 1991; 41, pages 1193-1196.
[26] N KOCH-HENRIKSEN, H BRONNUM-HANSEN, E STENAGER, Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry, in J Neurol Neurosurg Psychiatry, 1998; 65, pages 56-59.
[27] ML SUMELAHTI, PJ TIENARI, J WIKSTROM, TM SALMINEN, M HAKAMA, Survival of multiple sclerosis in Finland between 1964 and 1993, in Mult Scler 2002; 8, pages 350-355.
[28] H BRONNUM-HANSEN, N KOCH-HENRIKSEN, E STENAGER, Underlying cause of death in Danish patients with multiple sclerosis, in Brain, 2004; 127, pages 844-850.
[29] MD REDELINGS, L McCOY, F SORVILLO, Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001, in Neuroepidemiology, 2006; 26, pages 102-107.
[30] N GRYTTEN TORKILDSEN, SA LIE, JH AARSETH, H NYLAND, KM MYHR, Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway, in Mult Scler 2008; 14, pages 1191-1198.
31 C HIRST, R SWINGLER, DA COMPSTON, Y BEN-SHLOMO, NP ROBERTSON, Survival and cause of death in multiple sclerosis: a prospective population-based study, in J Neurol Neurosurg Psychiatry, 2008; 79, pages 1016 – 1021.
32 C SMESTAD, L SANDVIK, EG CELIUS, Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients, in Mult Scler 2009; 15, pages 1263-1270.

The study *The Prevalence of Multiple Sclerosis in Mures County* of 2013, published by the American Academy of Neurology (Antonio SCALFARI et al.), highlights the challenges that arise when discussing the causes of mortality in multiple sclerosis patients. Evidence shows that although MS is essentially chronic and invalid, long-term disability is not necessarily the immediate cause of death.

However, there is a risk of systemic complications arising in the advanced stages of multiple sclerosis, which can lead to death. Recording 'MS' as the main cause of death marks the attainment of the last step of the Extended Disability Status Scale (EDSS 10), defined as '... an acute death caused by a brainstem or respiratory system disease or death caused by a chronic medical condition leading to bed immobilisation and terminal pneumonia, sepsis, uraemia, cardiorespiratory failure.' This excludes the intermediate causes of death.

This definition can be interpreted variably by physicians and is completely unknown to those who are not familiar with MS, leading to a large variation in the proportion of 'MS deaths' in different study cohorts.

4 Epidemiology

At European level, epidemiological and demographic data from multiple sclerosis patients are subject to significant variations. Kingwell and his collaborators have conducted, in 2013[33] a systematic review of the literature for studies that include the prevalence and incidence of MS in European populations between 1985 and 2011. The main conclusion of this report is that estimates of these indicators are particularly heterogeneous at regional or country level.

The estimates on MS prevalence in the British Isles ranged from 96/100,000 inhabitants to over 200/100,000 inhabitants, with the highest estimates coming from Scotland and Northern Ireland. These two countries had the highest annual rates of incidence, ranging from 7.2 to 12.2 /100,000 inhabitants. With rare exceptions, the estimates on prevalence and incidence were higher in women (3:1 ratio). Epidemiological data at national level show significant discrepancies and geographical differences in available data, large areas in Europe being under-represented. Only 37% of the studies provided standardized estimates. For example, Sardinia registered a higher MS incidence and prevalence compared to the rest of Italy. Two out of six studies found an estimated MS prevalence of more than 100/100,000 inhabitants. One study had 69/100,000 inhabitants, but for 1985. In terms of MS incidence, Sardinia estimates of 3.4 to 6.8 per 100,000 are not even close to those observed across the entire Italian peninsula. Although prevalence and incidence estimates tended to be higher in the northern regions of the British Isles and in the northern countries, involving the epidemiological role of latitude, this model is not uniform, with higher estimates coming from southern Greece. Thus, the gross prevalence rate of MS cases increased between 1984 and 2006 from 10.1 in northeast Greece to 119.61 for 100,000 inhabitants. And the annual average rates of incidence increased between 1984 and 1989 from 2.71 to 10.73/100,000 inhabitants.

The epidemiology of multiple sclerosis in Romania is a subject of underdeveloped research, the literature presenting limited information for analysis. Existing studies provide contradictory data that are outdated[34][35][36] or do not meet geographical coverage criteria[37]. Therefore, the study proposed identifying and estimating the underlying epidemiological indicators needed to perform the cost analysis of multiple sclerosis.

4.1 Prevalence of multiple sclerosis in Romania

This study uses period prevalence as an epidemiologic indicator. This expresses the total number of cases of multiple sclerosis in Romania, without distinguishing between old and new cases during the reference year (2016). A systematic review of the literature was conducted to identify the prevalence of multiple sclerosis in Romania. The results indicate different values depending on the geographic coverage of the studies. In view of the many validity components (date of publication, limited geographical coverage, consultations with patient associations), the need to estimate prevalence was decided, using a method of calculation based on the use of services in the public system.

Table 3: Prevalence according to literature

Source	Prevalence	Year	Geographic coverage
Verdeș et al.	46.4/100,000 inh.	1978	Bucharest
Morariu et al.	22.2/100,000 inh.	1974	Transylvania
Bălașa et al.	26.1/100,000 inh.	2006	Mureș

[33] E KINGWELL, JJ MARRIOTT, N JETTE et al., Incidence and prevalence of multiple sclerosis in Europe: a systematic review, in BMC Neurol, 2013.
[34] WAITSUK P, WAGNER RC, KALMAN L, DULAU E - Incidence and forms of multiple sclerosis studied in the light of case reports of 22 years at the Neurological Clinics of Targu Mures in Neurol Psihiatr Neurochir 1968..
[35] MORARIU M, ALTER M, HARSHE M - Multiple sclerosis in Transylvania: a zone of transition in frequency in Neurology 1974.
[36] VERDES F, PETRESCU A, CERNESCU C - Epidemiologic survey of multiple sclerosis in the Bucharest city and suburban area in Acta Neurol Scand – 1978.
[37] BALASA R, FEIER C, DAN M, MOTATAIANU A, BALAIANU M, CHEBUTI C, CONSTANTIN V, BAJKO Z, PASCU I - *The Prevalence of Multiple Sclerosis in Mures County, Central Romania in Revista Romana de Neurologie*, Vol 2 No. 2, 2007.

In consultations for the multi-sclerosis patient pathway, physicians pointed out that most medical interactions appear in specialized outpatient centres. To obtain the number of these interactions, a data application was submitted to the National School of Public Health, Management and Healthcare of Bucharest (SNSPMPDSB). The data are summarized in the table below.

Table 4: The number of MS cases with access to the public health system

Diagnosis type	Denomination	Cases 2016 (records)	Individuals (CID) 2016
Main	G35 - Multiple sclerosis	2.649	2.628
Secondary	G35 - Multiple sclerosis	2.080	2.202
TOTAL		**4.729**	**4.830**

The data provided by SNSPMPDSB have been strengthened with the proportion of patients who do not have access to these services [38]. The number of resulting cases was converted according to the standard prevalence calculation formula, resulting in a value of **38.3 (over 7,500 cases)** of multiple sclerosis per 100,000 inhabitants for the reference year of the study. Of these, only about 5,000 accessed the public health system in the year 2016, therefore having an active disease. The reference population for the calculation of epidemiological indicators is the one reported to the National Institute of Statistics for the year 2016 (19,706,529 resident inhabitants).

This prevalence estimate, less than 5 cases per 10,000 population, classifies multiple sclerosis in the category of rare diseases, according to standards defined by the European Commission. This result is closer to the estimates of physicians and patients' representatives on the actual number of multiple sclerosis cases in Romania.

4.2 Incidence of multiple sclerosis in Romania

The number of new cases of multiple sclerosis reported in Romania in 2016 is the incidence of the disease over the reference period of the study. The value used in estimates was extracted from a recent response from the Romanian Ministry of Health to a parliamentary request.

For the reference year of the study, 965 new cases of multiple sclerosis were reported by physicians family in Romania, which represents an approximate incidence of **4.9 cases to 100,000 inhabitants**.

The Ministry's response also included an exact value for MS mortality in the reference year: **74 deaths (mortality rate 0.33).**

4.3 Demographic profile of patients

The profile of the Romanian patient with multiple sclerosis outlined based on the responses to an online questionnaire, has the following characteristics:

- mean age of 37 years;
- woman - only about 30% of patients are men in Romania;
- is regularly active on the labour market;
- diagnosed with multiple sclerosis about 5 to 10 years ago;
- that life changed for the worse after diagnosis with multiple sclerosis;
- is currently under immunomodulatory treatment

Multiple sclerosis is a difficult disease for patients of all ages. However, the impact may be stronger for the young population due to the critical periods of development that are affected. In the report *Young people with MS* conducted by the International Federation for Multiple Sclerosis, describes issues of self-esteem, education, social stigma, personal or professional development that a teenager or young adult can encounter in addition to the diagnosis of multiple sclerosis.

[38] KANAVOS P, TINELLI M, EFTHYMIADOU O, VISINTIN E, GRIMACCIA F, MOSSMAN J, The International Multiple Sclerosis Study (IMPRESS), Mar 2016 London School of Economics.

5 Patient pathway

5.1 Therapeutic options available

According to the Romanian therapeutic protocol for the treatment of multiple sclerosis, multiple sclerosis is the most disabling disease of the young adult [39], affecting over 7,500 patients and has important socio-economic implications, in addition to a severe deterioration in the quality of the patients' life.

Most treatments for MS are long-term, suppressing primarily the immune system. However, such suppressors of the immune system constitute increased risks of infections and cancer[40]. Alternative treatment options involve disease-modifying therapies such as interferons, glatiramer acetate, monoclonal antibodies, and sphingosine-1-phosphate receptor modulator [41]. These therapies have dramatically reduced the number of outbreaks and have slowed progression of the disease. Ultimately, inducing tolerance to autoantigens and restoring body homeostasis can effectively control disease.

Currently, the most commonly used treatment in national programs in Romania, for multiple sclerosis, is the immunomodulatory treatment. This treatment is intended for patients diagnosed with isolated clinical syndrome, multiple sclerosis - the relapsing-remitting form and in the initial stages of the secondary progressive form, as well as for relapses that may occur in progressive forms of the disease. This type of treatment is one of secondary prevention of severe disability (physical and mental), in patients with isolated clinical syndrome, multiple sclerosis (relapsing and remitting, and in secondary progression) since there is no known curative treatment for this condition, yet.

Cost-effectiveness studies have clearly highlighted that if immunomodulatory treatment is introduced as close as possible to the time of the clinical onset, preferably in the 'isolated clinical syndrome' stage, direct expenses (primarily those related to treatment with immunomodulators modifying the disease evolution) are significantly lower than if treatment is initiated in more advanced forms of disease.

The Romanian therapeutic protocol for treating multiple sclerosis indicates the following inclusion criteria of patients under immunomodulatory treatment:

- Certainity diagnosis of MS (MS clinically defined according to McDonald criteria), relapsing form-remitting or secondary progressive form;
- Clinically isolated syndrome with MRI changes characteristic of of MS (implying exclusion of other conditions that can manifest similar in clinical and imaging terms).

Therapeutic regimens in immunomodulatory therapy, indicated by the Romanian therapeutic protocol

The attending physician may choose as the first therapeutic solution, depending on the clinical form of MS and patient compliance, the following line I drugs: Interferon beta 1a, Interferon beta 1b, Glatiramer acetate, Teriflunomidum. The treatment initiated is continued as long as the patient responds to therapy and does not develop adverse reactions or therapeutic failure that require stopping or switching therapy.

Evaluation of therapeutic response is done by:

- Clinical examination every 3 months (or whenever clinical development requires it);
- Annual evaluation of EDSS score (or whenever clinical development requires it);
- Annual accounts of the number of clinical relapses;

[39] Appendix to the Order of the Minister of Health and of the chairman of the National Health Insurance House no. 475/308/2017 on the amendment and completion of the Order of the Minister of Health and of the chairman of the National Health Insurance House no. 1301/500/2008 approving the therapeutic protocols on prescription of drugs related to their international common denominations stipulated in the List of international common names for drugs received by insured persons, with or without personal contribution, based on a medical prescription, in the health insurance system, approved by Government Decision no. 720/2008 as of April 26th, 2017.
[40] M. INGLESE, M PETRACCA, Therapeutic strategies in multiple sclerosis: a focus on neuroprotection and repair and relevance to schizophrenia, in Schizophr. Res, 2015, 161, pages 94-101.
[41] Narges DARGAHI, Maria KATSARA, Theodore TSELIOS, Maria-Eleni ANDROUTSOU, Maximilian de COURTEN, John MATSOUKAS, Vasso APOSTOLOPOULOS, Multiple Sclerosis: Immunopathology and Treatment Update, in Brain Sciences, 2017, page 8.

- Annual MRI cerebral exam (at least in the first 2 years of treatment, then only when there are medical arguments justifying the indication).

The attending physician is the only one who can properly assess the response to therapy and may recommend continuing, changing or interrupting the treatment.

The failure of the immunomodulatory treatment consists in:

- The presence of 4 or more outbreaks per year (therapeutic failure to a form of immunomodulatory treatment - under treatment, a patient has 2 or 3 relapses in 6 months or at least 4 relapses in one year);
- Continuous progression of the disease;
- Severe side effects.

In case of failure of immunomodulatory treatment, consideration shall be given to:

- Discontinuation of immunomodulatory treatment;
- Change of the immunomodulatory drug;
- Change with line II drug, in the following situations:
    - in treatment, the patient has at least one clinical relapse, and the brain and spinal MRI indicates at least 9 new lesions on T2 images or at least 1 lesion with increased intake within one year
    - the disease has a continuous progression under the first line of treatment
- Associating other symptomatic drugs;
- Associating short-term corticosteroid therapy;
- Administration of an immunosuppressant.

The Romanian therapeutic protocol corresponding to the treatment of multiple sclerosis indicates that the prescribers of the treatment are physicians from the neurology specialty in the centres nominated for the national program of neurological diseases - multiple sclerosis.

5.2 Access and potential barriers to treatment

This section centralizes information on the access of multiple sclerosis patients to clinical and paraclinical services and to drugs. By Government Order no. 408/2010, MS patients are included in government-funded treatment schemes, and the services required to treat them are part of the basic care package provided by the National Health Insurance House (NHIH).

However, the public health infrastructure faces significant challenges that make it difficult to provide health care and with negative impact on the health of the population[42]. In addition to the public health literature, important qualitative data were collected from various actors in the system: physicians, patients, patients' representatives, hospital directors, and others.

Although infrastructure and staffing challenges are relatively common to all regions, their interaction with a number of specific socio-economic conditions may cause even more visible deficiencies for certain demographic categories. The most important issues identified in the allocation of resources at the health system level are:

- **Unsatisfied need for services**: the estimated level of access to diagnosis and treatment according to therapeutic protocols reported by patients with multiple sclerosis in Romania is 64%. This value is based on the responses of some MS patients in Romania in a larger study by the London School of Economics (IMPRESS, 2015) and it constitutes the only estimate for access. Due to a lack of studies in this area, the indicator used remains the only way to estimate the large differences in data on the number of patients accessing the health system (reported by the authorities) and the total number reported by patient associations and specialists in multiple sclerosis.

[42] Observatorul Român de Sănătate (2015) Hospistat 1.0 – Activitatea sistemului public de sănătate din România. București: Observatorul Român de Sănătate.

- **Significant inequalities of access between urban and rural areas**: the number of physicians and average health workers per capita in rural areas may be 10 times lower, comparing with the urban average, in counties like Mureș or Botoșani (Hospistat, Observatorul Român de Sănătate, 2012);
- **Polarization of national programs in university centres**: the delivery of the subsidized treatment by NHIH takes place in several urban centres that do not meet the demographic and geographical requirements of patients with multiple sclerosis.

In Romania, there are 12 medical units included in the National Program for Treatment of Neurological Diseases. These are distributed in 6 university cities and serve as treatment centres for patients with multiple sclerosis:

- **Bucharest:**
  - Bucharest Emergency University Hospital - Neurology Clinic;
  - "Dr. Carol Davila" Emergency Military Clinical Hospital of Bucharest - Neurology Clinic;
  - Colentina Clinical Hospital - Neurology Clinic;
  - Elias University Clinical Hospital - Neurology Clinic;
  - Fundeni Clinical Institute - Neurology Clinic;
  - "Prof. Dr. Alexandru Obregia" Psychiatrics Clinical Hospital of Bucharest;
  - "Prof. Agrippa Ionescu" Emergency Hospital of Bucharest - Neurology Clinic.
- **Târgu Mureș:**
  - Târgu Mureş County Emergency Clinical Hospital.
- **Iași:**
  - Iaşi Recovery Clinical Hospital.
- **Timiș:**
  - Timiş County Emergency Clinical Hospital - Neurology Clinic.
- **Cluj:**
  - Cluj County Emergency Clinical Hospital - Neurology Clinic.
- **Oradea:**
  - Oradea County Emergency Clinical Hospital.

According to the MS patient pathway in the public system and epidemiological data, patients are diagnosed and treated in medical institutions located near their home. Figures 2 and 3 (next page) highlight the suboptimal distribution of institutions that allow the distribution of treatment for multiple sclerosis within the national treatment program for neurological diseases.

Figure 2: Geographic distribution of treatment centres for multiple sclerosis included in The National Program for Treatment of Neurological Diseases[43]

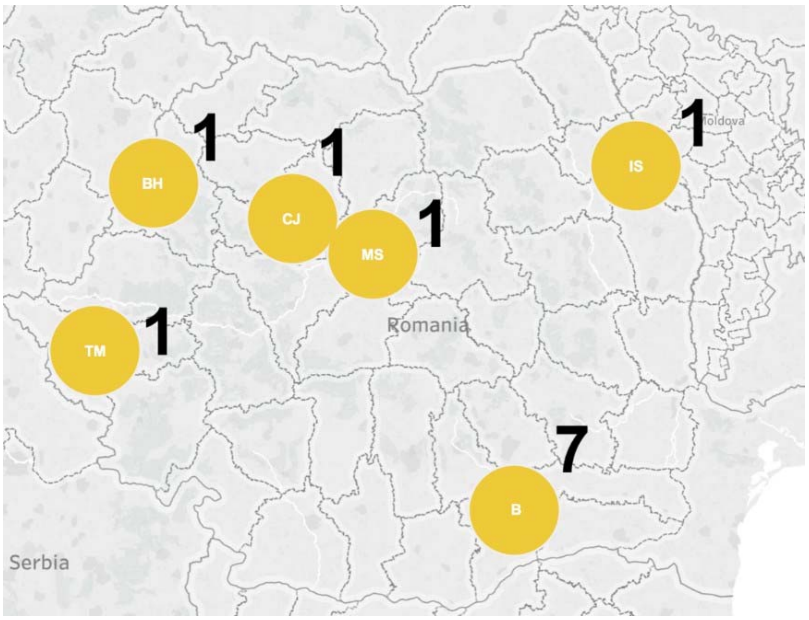
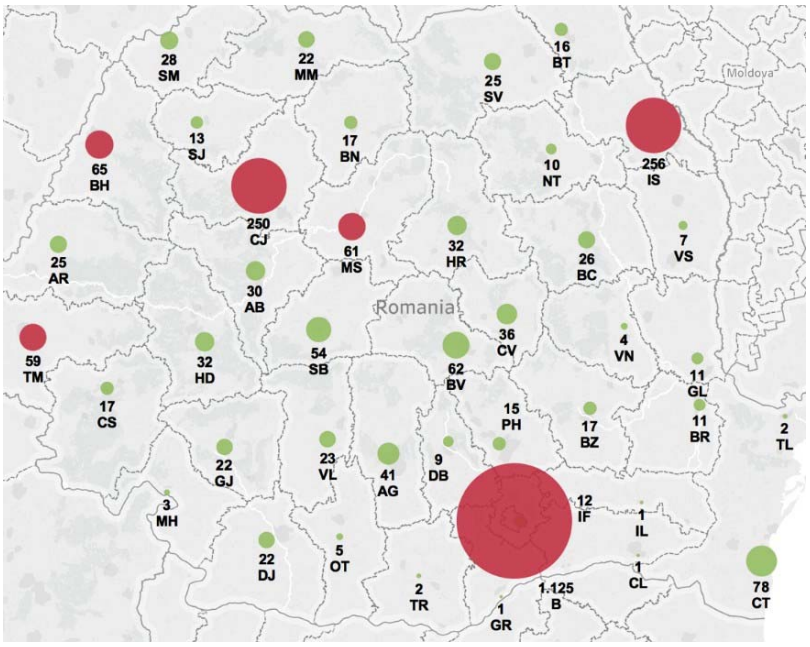


Figure 3: Geographic distribution of hospital admissions for Multiple Sclerosis[44]



The international multiple sclerosis study conducted by the London School of Economics also included Romania among the studied countries. The analysis concluded that there is an urgent need to provide better services for people with MS and the evidence suggests that this is possible if policy makers address three key issues:

- **Improving the quality of health care** and of health for every person suffering from multiple sclerosis;

[43] Source: Appendix to the Order of the Minister of Health and the Chairman of the National Health Insurance House no. 475/308/2017 for amendment and addition to the Order of the Minister of Health and the Chairman of the National Health Insurance House no. 1301/500/2008.

[44] Source: Public data from the Diagnosis Related Groups (DRG) funding system provided by the National School of Public Health, Management and Healthcare in Bucharest; in red - cities with centres included in the National Program for Treatment of Neurological Diseases; in green = institutions reporting cases of multiple sclerosis. The numbers are cases reported in DRG.

- **Generating solid evidence** (disease registers) to motivate decisions and change public policies that affect patients' quality of life;
- Increasing the **capacity** of the health system to **respond** to therapeutic innovations.

In an attempt to complete the literature, we developed a semi-structured questionnaire for patients with multiple sclerosis diagnosis. It included the following sections: (1) demographic information, (2) diagnostic and treatment, (3) social life, (4) workplace.

In total, 88 patients with multiple sclerosis completed the online questionnaire. The main barriers reported by the respondents were:

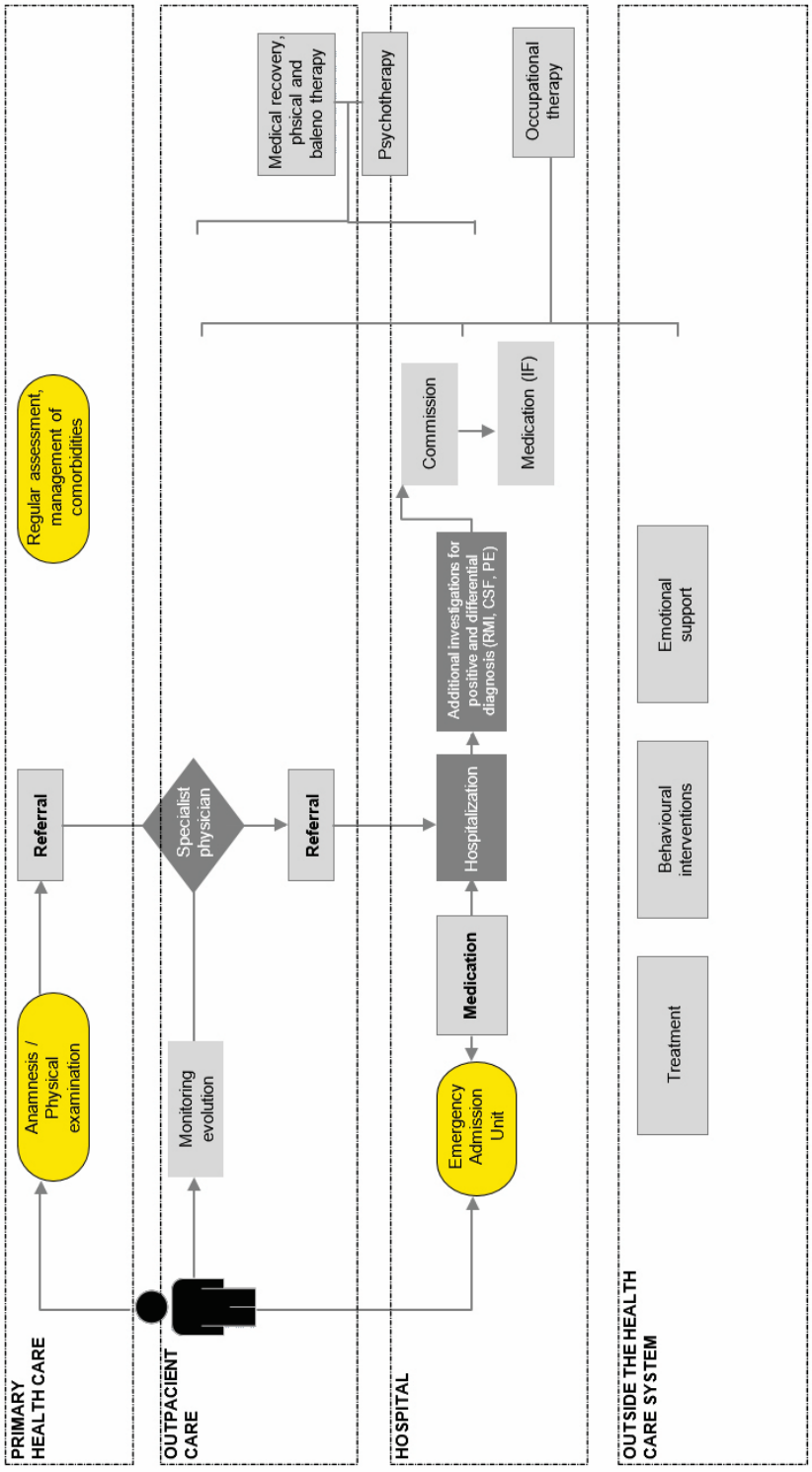
- Social stigma related to the disease;
- The frequent lack of medicines from the pharmaceutical market in Romania;
- Lack of service coverage for mental health comorbidities;
- Lack of medical staff interest in patients;
- Lack of communication between doctors and patients;
- Reduced number of centres in the national program;
- Barriers related to bureaucracy in the system;
- Lack of information about alternative medicines.

In terms of patient satisfaction, people with multiple sclerosis reported moderate overall satisfaction with the health system in Romania. This result is not an ideal indicator for the quality of care for these patients. Specialty literature describes cases where the low historical quality of medical services distorts patients' perception of today's conditions.

In other words, although patient satisfaction is quite high, this does not directly stem from the high quality of healthcare services but can be influenced by low patient expectations [45]. Several studies are needed to accurately measure the level of quality of medical services provided for patients with multiple sclerosis in Romania.

[45] WILLIAMS B, Patient Satisfaction: A Valid Concept?, in Social Science and Medicine, Feb 1994, 509-516.

Figure 4: Illustration of the pathway of multiple sclerosis patients in the Romanian health system [46][47]



[46] Appendix to the Order of the Minister of Health and of the chairman of the National Health Insurance House no. 475/308/2017 on the amendment and completion of the Order of the Minister of Health and of the chairman of the National Health Insurance House no. 1301/500/2008 approving the therapeutic protocols on prescription of drugs related to their international common denominations stipulated in the List of international common names for drugs received by insured persons, with or without personal contribution, based on a medical prescription, in the health insurance system, approved by Government Decision no. 720/2008 as of April 26th, 2017.

[47] At the time of elaboration of the study, the Commission of Experts working alongside the National Health Insurance House for the implementation of the National Program for Treatment of Neurological Diseases was still functional

6 Estimation of direct costs

6.1 Estimation of direct costs

The estimations of direct costs generated by multiple sclerosis are composed of cost categories that have been calculated using a 'bottom-up' methodological approach, starting from the multiple sclerosis therapeutic protocol. The exception to this rule applies to inpatient care, where data were extracted from national records.

Direct costs include:

- Costs with disease diagnosis and monitoring
- Costs with drug treatment
- Costs with clinical and paraclinical services
- Costs with the hospitalisation of patients
- Costs generated by comorbidities associated with the disease

The direct costs, estimated for 2016, amount to approximately **RON 272 million (EUR 60 million) in total** or **RON 56,500 (EUR 12,500)** per patient years. The direct cost per patient is 17 times higher than that for breast cancer patients[48].

The most important cost category is drug treatment, which accounts for 88% of total direct costs. The products settled through the national multiple sclerosis program amount to **5.7% of the budget for high-risk chronic diseases,** used in national curative programs reported by NHIH in the reference year of the study. The component associated with mental comorbidities has a similar contribution to the clinical and paraclinical services associated with the main disease. Hospitalization contributes little to direct costs (2% of the total), which is confirmed by the patient pathway.

Based on the median duration of MSBase disease (15.5 years), the average lifetime cost of a multiple sclerosis patient in Romania represents **RON 876,000 (EUR 193,000).** Of course, this estimate contains double diagnostic costs and other components that only appear once in a patient's lifetime.

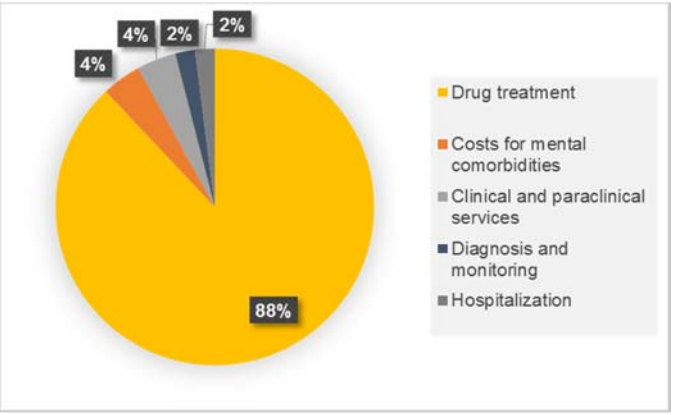
A detailed cost distribution is shown in the following table, as well as a percentage distribution in the following figure:

Table 5: Estimation of direct costs

No.	Cost category	Total 2016 (mill. RON)	Total 2016 (mill. EUR)
1	Drug treatment	238.80	52.7
2	Diagnosis and monitoring	5.80	1.2
3	Clinical and paraclinical services	10.80	2.4
4	Hospitalization	5.30	1.1
5	Costs with mental comorbidities	11.20	2.5
	TOTAL	**271.9**	**59.90**

[48] Coalition for Women's Health, Breast cancer burden in Romania, Benefits of investing in a screening program for breast cancer, Bucharest 2017.

Figure 5: Percentage distribution of direct costs



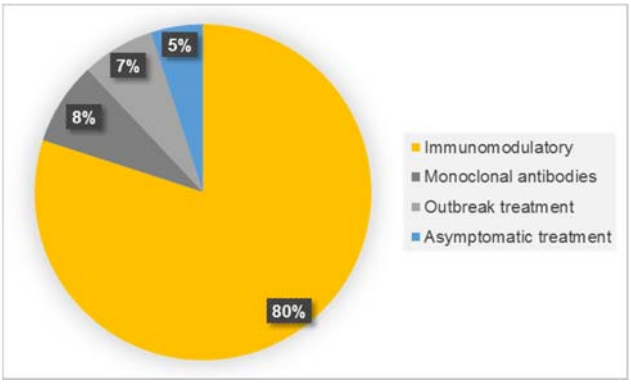
6.2 Drug treatment

The direct costs attributable to drug treatment were estimated using a 'bottom-up' approach, starting from the multiple sclerosis therapeutic protocol. In the first phase of the analysis, a list of recommended drugs was developed along with their therapeutic indication. The prices for these products from Appendices no. 1 and 2 of the Order of the Minister of Health and of the Chairman of the National Health Insurance House no. 1605/875/2014 approving the calculation method, the list of the trade names and the settlement prices of the medicinal products granted to the patients under the national health programs and their calculation methodology of December 23rd, 2014 and the national catalogue of drugs (CaNaMed).

The weighted average cost per patient is based on several assumptions, depending on the type of treatment. First, the share of patients undergoing immunomodulatory treatment (79%) and that of patients requiring symptomatic treatment (67.9%) was extracted from the patient survey. Secondly, the average number of acute episodes per year was calculated using an estimate of the literature[49]. The number of patients requiring symptomatic treatment was also estimated using the questionnaire.

The estimated total cost of drug treatment in multiple sclerosis patients from Romania is **RON 238.8 million (EUR 52.7 million)** in 2016 for the number of patients reported by NHIH in national programs (3930). More than three-quarters of these costs are estimated to be attributable to immunomodulatory treatment.

Figure 6: Distribution of drug costs among patients with multiple sclerosis [50]



The total cost per patient, according to our analysis is approximately **RON 49,500 (EUR 11,000) per patient** for the year 2016. In the same year, the National Health Insurance House has declared a cost per patient in the national program of **RON 31,687**.

[49] LHERMITTE F, MARTEAU R, GAZENGEL J, DORDAIN G, DELOCHE G - *The frequency of relapse in multiple sclerosis* in Zeitschrift fur Neurologie in 1973.
[50] Source: estimates from the current study for the reference year.

The difference between the estimated value and the costs of this program may be attributed to problems with access to NHIH services or to payments from the patients' pockets.

6.3 Diagnosis and monitoring costs

Diagnosis and monitoring costs were estimated 'bottom-up', using the therapeutic protocol and the qualitative data of the study to estimate annual mean values. The rates for services settled through NHIH were calculated by multiplying the scores stipulated in the NHIH framework contract with their value from the last quarter of 2016. The indicators used as multipliers were: the annual incidence of diagnosis and the number of day hospitalization records for monitoring patients with multiple sclerosis.

On an average, the diagnosis of multiple sclerosis costs **RON 2,293 RON per patient**, and annual monitoring is **RON 750**. An important observation is that these amounts per patient are estimated by the NHIH's reimbursement rates. From the diagnosis component, the most important cost component is paraclinical services (approximately 90% of the total). A detailed explanation of these costs is available in the table below:

Table 6: MS diagnostic and monitoring costs

Cost category	NHIH rate	Quant/Pac.	Total/ Patient	Total Patients	Value (RON)
Clinical services	**RON**	**Estimates**	**RON**	**Estimates**	**RON**
Fee for service- primary medicine	12.65	1	12.65	965	12.207
Neurological examination - initial	23.76	1	23.76	965	22.928
Radiological examination	23.76	1	23.76	965	22.928
Neurological examination – evoked potential	23.76	1	23.76	965	22.928
Differential diagnosis examination	31.68	1	31.68	965	30.571
Confirmation examination - Neurology	23.76	1	23.76	965	22.928
Payments per capita			**139.37**	**Subtotal**	**134.492**
Primary medicine payment/capita	34.63	1	34.63	965	33.418
Paraclinical investigations			**34,63**	**Subtotal**	**33.418**
Laboratory	750	1.5	1125	965	1.085.625
Potential claimed	88	1	88	965	84.920
MRI	700	1	700	965	675.500
Lumbar puncture	126	1	126	965	121.590
CSF analysis	80	1	80	965	77.200
Monitoring			**2119**	**Subtotal**	**2.044.835**
MRI	700	1	700	4.729	3.310.300
Radiological examination	23,76	1	23,76	4.729	112.361
Neurological examination	23,76	1	23,76	4.729	112.361
				Subtotal	**3.535.022**
TOTAL					**5.747.767**

6.4 Costs with clinical and paraclinical services

Similar to diagnosis and monitoring, outpatient care costs were estimated 'bottom-up' using the therapeutic protocol and qualitative data from the study to estimate annual mean values**.**

The rates for NHIH settled services have been calculated by multiplying the scores stipulated in the framework agreement, according to their value from the last quarter of 2016.

The indicators used as multipliers were the number of hospitalization records for monitoring patients with multiple sclerosis. An estimated total of approximately **RON 11 million** (EUR 2.4 million) comprises the direct costs with clinical and paraclinical services for multiple sclerosis patients.

A detailed explanation of these costs is available in the following table:

Table 7: Costs with clinical and paraclinical services

Cost category	NHIH rate	Qty. /Pac.	Cost /Pac.	Multiple	Value (RON)
Clinical services	**RON**		**RON**	**NHIH**	**RON**
Neurological examination	23.76	1	23.76	4.729	112.361
Paraclinical services				**Subtotal**	**112.361**
Laboratory	187.8	1,5	281.7	4.729	1.332.159
MRI	700	1	700	4.729	3.310.300
Recovery services				**Subtotal**	**4.642.459**
Rehabilitation session	33	12	396	4.729	1.872.684
Monthly rehabilitation ceiling	42	21	882	4.729	4.170.978
				Subtotal	**6.043.662**
				TOTAL	**10.798.482**

6.5 Hospitalization costs

Hospitalization costs were estimated using an automated data collection process from the website www.drg.ro. Annual data from 181 hospitals reporting in the DRG system for the codes associated with multiple sclerosis (B3091 and B3092) have been filtered and classified according to the type of cases identified (acute or chronic). A mixed approach was used to differentiate from acute and chronic funding schemes for hospitals.

The cost was calculated based on the weighted-rate per mean case (WRC) hospital financing system, for acute cases. The relative service value (RV) was multiplied by WRC, and the case-specific rate (CR) was derived for each hospital. This rate was then multiplied by all acute cases associated with multiple sclerosis from the hospital in question. For chronic patients, the cost was calculated based on the number of hospitalization days, multiplying this value by the annual reference rate for this type of service.

The total cost for hospital care in 2016 was about **RON 5.1 million (EUR 1.1 million)**, **of which** 84% for patients classified as acute and 16% for chronic patients. A total of 2,577 patients with multiple sclerosis were admitted to hospitals in Romania in 2016, of which 2085 cases in acute departments (average reimbursement fee RON 2,107) and 492 cases in chronicle departments (average rate settled, RON 1,733).

6.6 Comorbidity costs

For costs associated with multiple sclerosis comorbidities, it is essential to isolate these diseases from the main diagnosis, in this case multiple sclerosis. Some comorbidities occur independently of the disease studied, others are the result of such disease. The literature describes examples of diseases for which multiple sclerosis cannot be isolated as an excess factor of comorbidity costs[51].

One such example is diabetes, for which it was found that the involvement of comorbidity in multiple sclerosis cost studies has a disproportionate impact on total costs. Other prevalent comorbidities, which may also raise direct values in cost studies, are cardiovascular disease (hypertension, dyslipidemia, arrhythmias, stroke), respiratory disease (chronic bronchopneumopathy), gastroenterological disease (irritable bowel syndrome, viral hepatitis)[52].

For this study, only two comorbidities were included (depression and anxiety) because of availability of accurate data on the excess risk of developing these diseases among patients with multiple sclerosis. This can be explained by the greater prevalence of comorbidities among patients with multiple sclerosis.

The cost of comorbidities was estimated by the attributable risk method[53]. In this study, attributable risk or excess risk is the prevalence of comorbidities among a healthy population and the multiple sclerosis population. To calculate the proportion of cases in this population, where multiple sclerosis has played a causal role in the development of mental comorbidities, etiological fractions of the disease were calculated. In the absence of cost studies for depression and anxiety in Romania, said values were estimated using studies with similar methodology in Germany and the direct cost of multiple sclerosis in this study, as well as epidemiological data for Romania [54] [55] [56].

The total value for excess depression and anxiety costs among multiple sclerosis patients in Romania in 2016 was approximately **RON 11.2 million (EUR 2.5 million).** Clinical depression records twice as high costs as compared to anxiety.

Table 8: Annual cost of comorbidity for patients with multiple sclerosis

Cost Component	Risk Rel.	Excess risk	Sclerosis cost RO	Relative cost in the literature	Weight of calculation	Number of cases with comorbidities	Value (RON)
Mental comorbidities							
Depression	0.50	1.25	53960	0,16021	0.11	849.02	7.339.705
Anxiety	0.33	1,45	53960	0,09484	0.10	754.49	3.861.315
TOTAL							**11.201.020**

[51] ERNSTSSON O ET AL, Cost of Ilness of Multiple Sclerosis - A systematic review, in Plos One, Jul 2016.
[52] A M RUTH, J COHEN ET AL., A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview, in Multiple Sclerosis, 2015
53 GEFELLER O, An Annotated Bibliography on the Attributable Risk, in Biometrical Journal, 1992.
54 KOBELT G, BERG J, LINDGREN P, ELIAS WG, FLACHENECKER P, FREIDEL M, KONIG N, LIMMROTH V, STREUBE E, Costs and quality of life of multiple sclerosis in Germany, in European Journal of Health Economy, Sep 2006.
55 ANDLIN-SOBOCKI P, WITTCHEN HU, Cost of affective disorders in Europe, in European Journal of Neurology, Jun 2005.
56 PETRACHE D, FILIP I, TĂNASE C, Epidemiologia Depresiei, in Revista Medicală Română, Volume 62, No. 3, 2005.

7 Estimation of indirect costs

7.1 Estimation of indirect costs

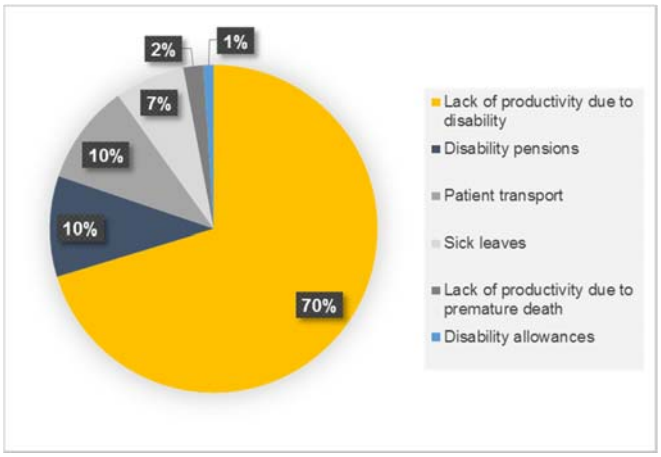
The estimations of indirect costs consist of cost categories that have been calculated through a mixed 'bottom-up' approach for transport, medical leave, disability benefits, disability pensions and disease burden indicators for disability, and premature death.

The indirect costs, associated to multiple sclerosis, for 2016, amount to approximately **RON 140.5 million (EUR 31 million) in total** or **RON 29,000 (EUR 6,500)** per patient. A detailed cost distribution is shown in the following table, as well as a percentage distribution in the following figure:

Table 9: Annual indirect costs in patients with multiple sclerosis in Romania

No.	Cost category	Total 2016 (million RON)	Total 2016 (million EUR)
1	Lack of productivity due to disability	100	22
2	Lack of productivity due to premature death	2.8	0.6
3	Disability pensions	14	3.1
4	Disability allowances	0.8	0.2
5	Sick leaves	9.4	2.1
6	Patient transport	13.5	3
	TOTAL	**140.5**	**31.00**

Figure 7: Percentage distribution of indirect costs



7.2 Productivity losses caused by disability and premature death

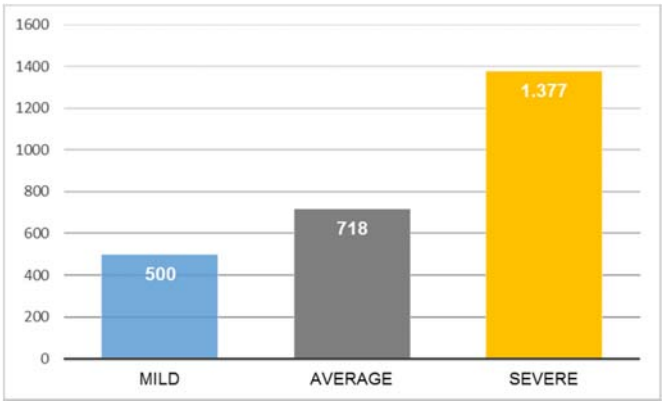
To estimate the cost of premature mortality for multiple sclerosis and associated disability, the Years of Life Lost (YLL) and Years of Life with Disability (YLD) indicators were calculated for the active population and the result was multiplied with Romania's GDP per capita in the reference year.

Table 10: Calculating the YLD indicator for multiple sclerosis patients (prevalence approach)

Severity	Cases	Disability weight	YLD
Mild	2,733	0.183	500
Average	1,550	0.463	718
Severe	1,915	0.719	1,377
TOTAL			**2,595**

YLD was calculated by weighing cases by severity with disability weights extracted from the Global Burden of Disease study from the World Health Organization. For the reference year 2016, the total number of years lost due to disability (YLD) in multiple sclerosis patients in Romania was **2,595**, with an indirect productivity cost of approximately **RON 100 million (EUR 22 million).**

Figure 8: Years of life with disability, depending on the disease severity



The number of years lost due to mortality (YLL) was calculated based on the mortality associated with multiple sclerosis reported by the Ministry of Health in Romania. In 2016, the indirect cost of productivity attributable to MS mortality was approximately **RON 2.8 million (EUR 0.6 million)**. This result is in line with WHO estimates for YLL and YLD for multiple sclerosis in Romania. The significant cost difference in favour of YLD is explained by the limited impact of the disease on the life expectancy of individuals.

7.3 Indirect costs of disability pensions

The Ministry of Labour and Social Justice ensures the payment of disability pensions [57][58].

According to the survey questionnaire, 58% of the sample is eligible for disability pension. To calculate the annual costs with these pensions, the total number of cases eligible, in terms of age, having this ratio and the average disability pension value, in the reference year, have been multiplied. In total, approximately **RON 14 million (EUR 3.1 million)** have been subsidized for patients with multiple sclerosis as disability pension.

[57] Law no. 263/2010 on the unified public pension system, as further amended and supplemented.
[58] Order no. 2272/2013 approving the Procedure for implementation of the provisions of art. (42) of Law no. 448/2006 on protection and promotion of the relevant rights of disabled persons, corroborated with those of art. 77 of the Law no. 263/2010 on the unified public pension system; Law no. 263/2010 on the unified public pension system.

Table 11: Indirect annual costs of disability pensions for patients with multiple sclerosis

Cases	Ratio of the eligible patients for retirement	Mean disability pension for the year 2016 (RON)	Months	Total
3.465	58%	579	12	13.963.395

7.4 Indirect costs of disability allowances

The Ministry of Labour and Social Justice ensures the payment of disability benefits granted to individuals diagnosed with multiple sclerosis [59] [60]. In view of the scientific validity of the study, a request for information was submitted on the detailed value of disability allowance per severities (severe, accentuated, and environmental) to people diagnosed with multiple sclerosis. The application was submitted to the Ministry of Labour and Social Justice, the National Authority for Disabled Persons, and the National Payments and Social Inspection Agency

The National Authority for Disabled Persons was the institution that made the following answer[61] to the request for information: *In accordance with the provisions of the Government Decision no. 989/2014 regarding the updating of the amount of social benefits stipulated in art. 58, paragraph of the Law no. 448/2006 on the protection and promotion of the rights of persons with disabilities, starting with January 1st, 2015, they had the following values:*

- for an adult with severe disability RON 340:
  - RON 234 monthly allowance;
  - RON 106 complementary monthly budget.
- for an adult with accentuated disability RON 272:
  - RON 193 monthly allowance;
  - RON 79 complementary monthly budget.
- for an adult with average disability RON 39:
  - RON 39 complementary monthly budget.

The indirect costs of these allowances were calculated according to the patients' answers to the survey questionnaire. Several categories of severity were weighted by the share of eligible applicants for this type of allowance. Annual costs are approximately **RON 800,000 (EUR 200,000)**.

Table 12: Indirect annual cost of disability allowances for patients with multiple sclerosis

Type/Severity	Mild	Average	Severe
Allowance	0	193	234
Complementary budget	39	79	106
Subtotal	39	272	340
Eligibility proportion	42%	26%	32%
Cases	1.855	1.128	1.394
TOTAL (RON)	**72.332**	**306.854**	**474.090**

[59] Law no. 263/2010 on the unified public pension system, as further amended and supplemented.
[60] Order no. 2272/2013 approving the Procedure for implementation of the provisions of art. 42) of Law no. 448/2006 on protection and promotion of the relevant rights of disabled persons, corroborated with those of art. 77 of the Law no. 263/2010 on the unified public pension system; Law no. 263/2010 on the unified public pension system.
[61] According to the request addressed to the National Authority for Persons with Disabilities, registered with no. 4129/April 16th, 2018..

7.5 Indirect costs for sick leaves

To estimate the costs associated with sick leave for multiple sclerosis, cases were selected at an active age classified by severity and occupancy rate according to the online questionnaire. It was assumed that believed that patients with severe disabilities are predominantly incapable of work. The resulting value was multiplied by the average number of days of leave per year, based on two degrees of severity (mild and moderate), extracted from the answers to the questionnaire applied in the study. The final result was reported to the gross average wage in the reference year of the study.

Approximately 2,650 patients were included in the estimate with a total of 74,000 days of sick leave. The total estimated cost for sick leave is approximately **RON 9.4 million (EUR 2.1 million)**, for the year 2016.

7.6 Transport costs

Patients with multiple sclerosis travelled approximately **8.5 million of km** per year as a result of medical visits, with an estimated cost of **RON 13.5 million (EUR 3 million)** in the year 2016, namely approximately **RON 2,018 (EUR 445)** per patient years.

The table below shows the average of the distance travelled to each centre, multiplied by the average number of visits per year reported in patient questionnaires and the number of patients in the area (estimated from the prevalence and population of the service area, assuming a uniform geographical distribution). The tariff per km was estimated at the value of a taxi in Bucharest, for two reasons. Firstly, as a result of disability, multiple sclerosis patients require increased comfort and support from an attendant for these travels[62]. Also, the literature recommends that all costs associated with a car (investment depreciation, tires, fuel, oil, civil liability insurance, vignette, fully comprehensive car insurance policy) be included in the real cost calculation per kilometre. In this case, the values are well above the commercial price of many transport alternatives (3.7 RON/km)[63].

Table 13: Annual transport costs for patients with multiple sclerosis

Centre	Distance average	Average travels	Population coverage	Reduction for resid. population	Cases	Total KM	Rate/KM	Value (RON)
B	102.47	5.6	8,149,273	6,265,848	2,575	2956412	1.6	4,730,259
BH	39.83	5.6	907,126	710,759	292	130,357	1.6	208,571
CJ	69.27	5.6	2,003,101	1,678,525	690	535,400	1.6	856,641
IS	132.01	5.6	4,107,017	3,786,129	1556	2,301,398	1.6	3,682,237
MS	129.03	5.6	2,008,299	1,874,009	770	1,113,395	1.6	1,781,432
TM	153.22	5.6	2,382,301	2,064,641	848	1,456,619	1.6	2,330,591
TOTAL						**8,493,583**		**13,589,733**

In the absence of access to patient residence data, we used the hospital where patients receive care as an indirect indicator for their home. Hospital data collected for the estimation of direct hospital costs were used for this analysis. Therefore, its purpose was to estimate the additional distance travelled by patients with multiple sclerosis to benefit from the treatment set out in the national program (Figure 3).

We used counties in the proximity of MS centres to build theoretical catchment areas for the MS national centres. Using an automated algorithm, the distances between each hospital where multiple sclerosis patients were admitted and the closest centre included in the national multiple sclerosis program.

[62] Multiple Sclerosis Trust, Great Britain, section Driving and Transport 2018, available at https://www.mstrust.org.uk/a- z/driving-and-transport.
63 How to calculate cost per km, Gala Transit Conference, section Passenger Transport, 2012

8 Evolution of the number of patients (2018 - 2028)

The prevalence of MS is defined for the purpose of this model as the number of cases that accessed the public system in Romania. It is calculated, for each year, based on the data of the previous year, using the following formula, with the reference year values of the study (2016):

$$P(n) = P(n-1) + I \times A - M,$$ where:

P = prevalence, n = reference year, I = incidence, A = access to the system, M = mortality.

Important prerequisites:

- The access of patients with MS in the public system will progressively increase from 64% to 80% in the following 10 years;
- Access to the national program will increase from 74%, 1% per annum, with capping to 85%;
- Incidence will decrease from ~5/100,000 inhabitants to epidemiological estimates of 1.7 / 100,000 inhabitants until 2020;

  According to the values in neighbouring countries [64], following the implementation of the National Health Development Strategy 2014-2020 [65]. At this time, the increased incidence is explained by the diagnosis process in on-going reform (better MRI devices, better services);

- MS prevalence will increase by approximately 2% per year, in line with global trends;
- MS will remain a rare disease in Romania (prevalence below 50/100,000);
- Mortality is adjusted for increases in prevalence;
- The population of Romania will remain constant;
- The demographic structure of the MS population will remain constant.

In 2010, there will be **9,349 cases of MS** in Romania, comprising a prevalence of **47.44/100,000 inh.**

Table 14: Estimation of the multiple sclerosis patients' evolution in Romania

	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Total patients in the system	4830	5331	5703	5946	6092	6244	6403	6567	6737	6914	7096	7285	7479
Patients with access to the national program	3586	3998	4334	4578	4752	4933	5122	5319	5525	5738	5961	6192	6357
Mortality	74	75.1	76.2	77.2	78.2	79.3	80.3	81.3	82.3	83.4	84.4	85.4	86.4
Incidence	965	900	700	500	351	351	351	351	351	351	351	351	351
Proportion, access to the national program	0.74	0.75	0.76	0.77	0.78	0.79	0.8	0.81	0.82	0.83	0.84	0.85	0.85

[64] E KINGWELL ET AL., Incidence and prevalence of multiple sclerosis in Europe: a systematic review, in BMC Neorology, 2013
65 Ministry of Health - National Health Strategy 2014-2020 - http://www.ms.ro/strategia-nationala-de-sanatate-2014-2020/

9 Final observations

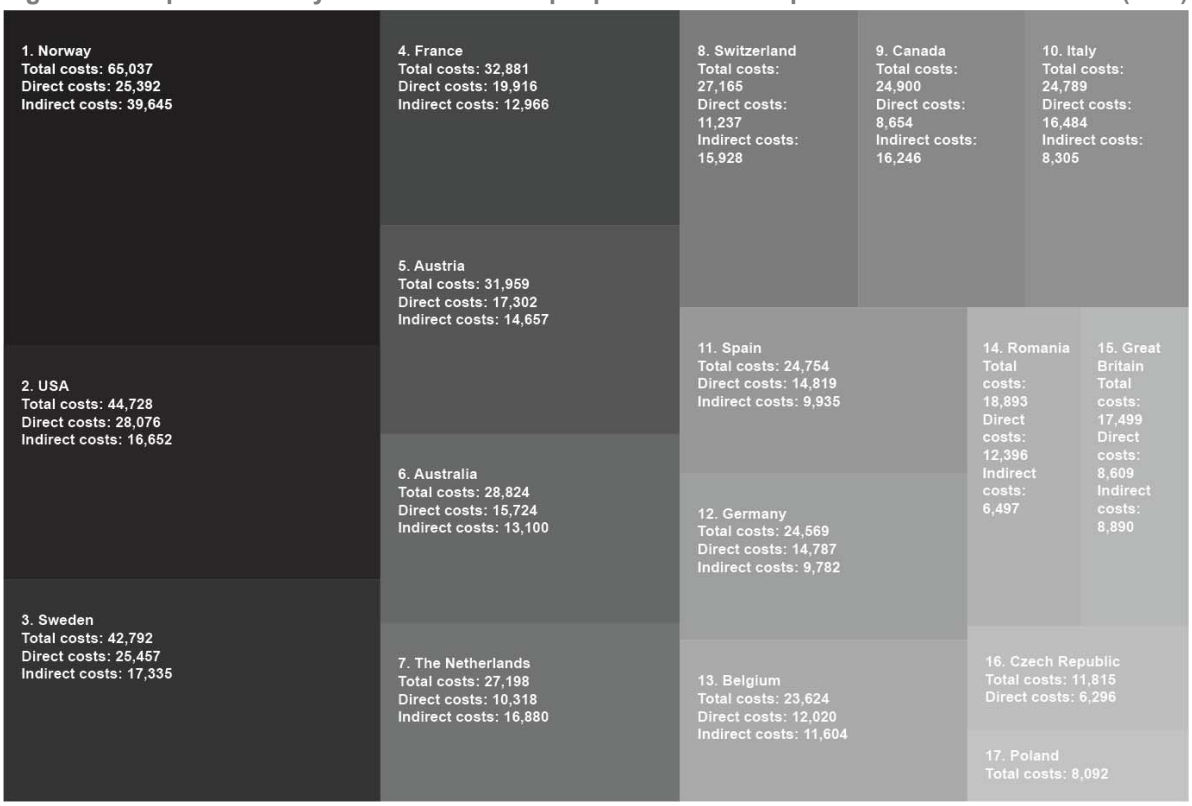
The total costs with multiple sclerosis estimated in this report are **RON 412.5 million (EUR 91 million),** for the reference year 2016, namely approximately **RON 85,500 (EUR 19,000)** per patient. From this amount, 66% of the total costs of multiple sclerosis in Romania in 2016 are due to the direct costs for diagnosing, treating and monitoring this disease, while 34% of the total costs of the disease are indirect costs.

The most important reference for cost studies in multiple sclerosis is a systematic review from of 2016 published by Olivia Ernstsson et al. from Karolinska Institutet. This analysis includes 29 multiple sclerosis disease cost studies. Based on the comparison of the results of this study with similar methodological approaches, we conclude that:

- The total annual cost of multiple sclerosis is within the minimum and maximum ranges present in the literature. From the 29 studies analysed, which included 17 countries in Europe, together with the United States, Canada and Australia, Romania ranks 14th, before Poland, the Czech Republic and Great Britain.

For this analysis, one must bear in mind that many of these studies use different scientific methodologies. Some authors differentiate between direct and non-medical costs (e.g. other disease-related payments for patients). In order to maintain data comparability, direct non-medical costs were excluded from total direct costs if this breakdown had occurred.

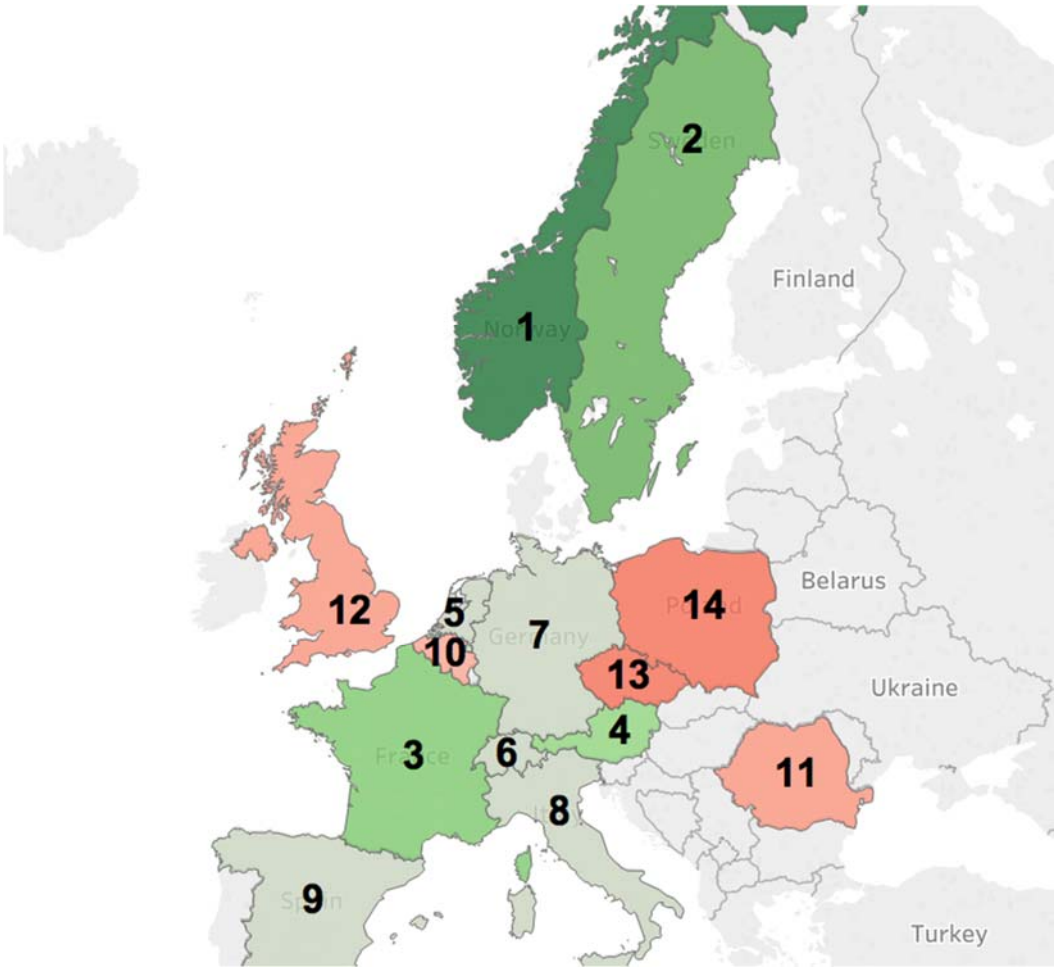
Figure 9: Comparative analysis of annual costs per patient with multiple sclerosis in the literature (EUR)



- At European level, Romania ranks lower in the top for indirect costs (12th place) than in direct costs (8th place).

Considering total costs, Romania ranks 11th at European level from among 14 studied countries, significantly under the Nordic countries, which allocate on average more than twice as many financial resources for services provided to patients with multiple sclerosis. This result is also reflected in the health expenditure in Romania, which was in the reference year of the study, at about 5% of GDP. An essential observation is that these values are dependent on the efficiency of the healthcare system in each country. Lower direct cost can mean both a lower quality of life for patients with multiple sclerosis and an effect of better treatment strategies and early diagnosis of the disease - which reduce system cost, on the long run. So, these comparisons give the outcomes of the study a perspective, but they have to be interpreted with the exception of these complexities.

Figure 10: Ranking map for the total annual cost per patient with multiple sclerosis from the European Union countries (EUR)



Finally, it should be noted that some of the basic values used in this study are estimates of missing indicators from the literature. The absence of multiple sclerosis patient registries in Romania excludes the possibility of extracting valid data on epidemiological *indicators* (prevalence, incidence, mortality, severity), *demographic information* (occupancy level, activity level, anthropometric indices), *specific information about the pathology* (treatment, access to the health system) or data on *intangible costs of the disease* (costs for the family, emotional distress).

The lack of this information and the presence contradictory values (epidemiological studies vs. reports of the Ministry of Health) in the literature have an important impact on the validity of projections regarding the evolution of the patients number to be treated in the period 2018-2028. For more information on the limitations of the study, please refer to methodological appendices.

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