ReMuS MULTIPLE SCLEROSIS PATIENT REGISTRY

Regular Output from ReMuS Registry

Data export updated on 30. 6. 2016

– Summary Report

In Prague, 27th September 2016

Endowment fund IMPULS
Kateřinská 30, Praha 2, ID: 26169428
www.multiplesclerosis.cz

Contents

1 Introduction

National Multiple Sclerosis Patient Registry (ReMuS) was mainly created to obtain data on the occurrence, incidence and clinical course of multiple sclerosis (MS), its clinical symptoms, MS relapse frequency rates, disease progression, MS treatment, disability development, comorbidities and causes of death. The objective is to provide outputs for cost and effectiveness monitoring of health care and medicinal preparations, evaluation of information to be provided to health care payers, other public institutions and medicinal preparation manufacturers, further to assess the severity of MS and its socioeconomic impacts, and to facilitate the creation of outputs for scientific and statistical purposes.

Based on acquired data, it will be possible to look for possible risk factors both for the occurrence of MS itself and lack of effectiveness of treatment or more rapid progression of the disease. Information on course of MS will enable health care payers to better plan the financial means necessary for the treatment of this disease. Information on treatment effectiveness is instrumental in improving therapeutic choices and implement changes or modifications when relevant.

The registry now includes, in this first phase, only multiple sclerosis patients who:

- undergo treatment in one of the participating MS treatment centres
- have received one of the DMDs (disease modifying drugs) preparations (i.e. disease progression modifying treatment) or IVIGs (intravenous immunoglobulins) any time after 1. 1. 2013,
- have signed informed consent with processing their personal and clinical data in ReMuS registry.

Detailed analysis included only patients who had the record in the registry from the first half of the year 2016.

2 Results

As of 30. 6. 2016, ReMuS registry included data of patients from fourteen MS treatment centres – General University Hospital in Prague (VFN), Hospital in Teplice, Hospital in Jihlava, University Hospital Motol in Prague, University Hospital in Plzeň, Hospital of Pardubice Region, University Hospital in Ostrava, University Hospital Královské Vinohrady in Prague, Thomayer University Hospital Krč in Prague, University Hospital in Hradec Králové, University Hospital in Brno (Bohunice), University Hospital in Olomouc, Hospital in České Budějovice and Regional Hospital T. Baťa in Zlín. The analysis included, according to previous agreement, data of patients who were treated in the period from 1. 1. 2013 with one of the DMD and IVIG preparations reported below and also had available actual data:

- DMDs – Aubagio, Avonex, Betaferon, Copaxone[20], Copaxone[40], Extavia, Gilenya, Lemtrada, Rebif[22], Rebif[44], Tecfidera, Tysabri
- IVIGs – Endobulin, Flebogamma, Gammagard, Kiovig, Octagam.

Table 1 included the final number of patients included in ReMuS registry as of 30. 6. 2016. In the first column it is shown the total number of patients in the registry (patients fulfil the condition of informed consent and DMD or IVIG treatment). In the second column it is shown the number of patients with actual data (last visit from the first half of the year 2016) included in the current half-year analysis.

Table 1 Total number of patients by centres

Centre	Patients in the registry	Analysed patients	Percentage in the analysis
VFN	2117	2065	24,7%
Teplice	874	847	10,1%
Jihlava	265	260	3,1%
Motol	1011	981	11,7%
Plzeň	499	487	5,8%
Pardubice	462	448	5,4%
Ostrava	848	828	9,9%
Vinohrady	434	416	5,0%
Krč	300	293	3,5%
Hradec Králové	791	772	9,2%
Brno Bohunice	356	347	4,2%
Olomouc	183	176	2,1%
Č. Budějovice	398	386	4,6%
Zlín	47	47	0,6%
Total	8585	8353	100,0%

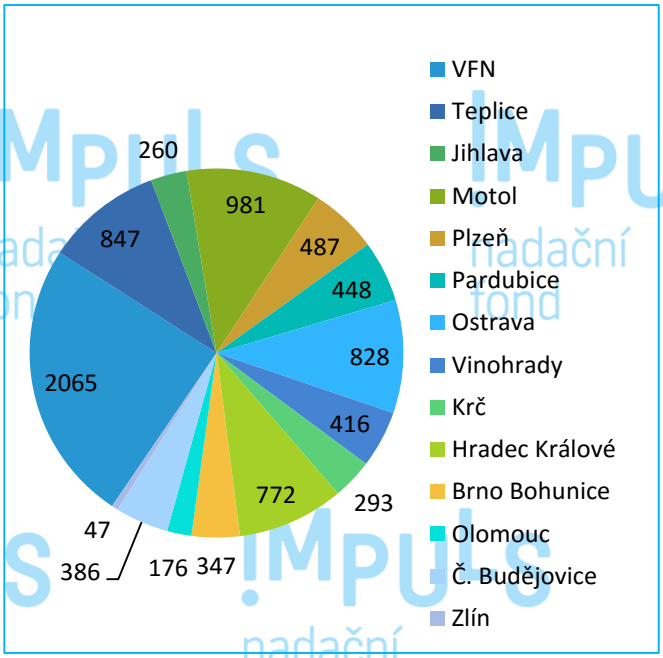

Figure 1 Total number of analysed patients by centres

The table and figure below illustrate the development of the number of patients and centres participating in ReMuS registry from the creation of the registry till present. The first data export in summer 2013 analysed data originating from three centres - a total of 1 501 patients. Now, in June 2016, the registry has expanded to include 14 MS treatment centres already, so the data of 8 353 patients from the whole of the Czech Republic enter analysis.

Table 2 Number of patients in the ReMuS registry - development

Data export date	Number of centres	Number of patients to be analysed
30. 06. 2013	3	1 501
31. 12. 2013	7	2 920
30. 06. 2014	12	4 715
31. 12. 2014	12	5 639
30. 06. 2015	13	7 099
31. 12. 2015	13	7 786
30. 06. 2016	14	8 353

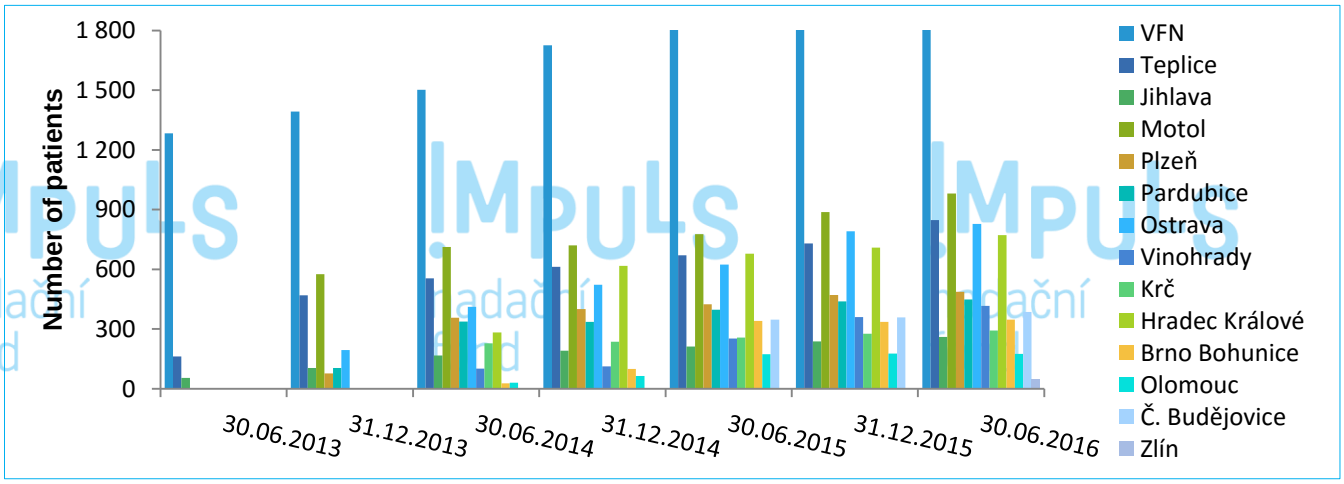

Figure 2 Number of patients in the registry contributed by individual centres - development

2.1 Demographic data

2.1.1 Sex

Taken together, all centres treat 71,5 % women and 28,5 % men.

Table 3 Patient distribution by sex

Sex	All centres	
	Number	Percentage
Females	5971	71,5%
Males	2382	28,5%

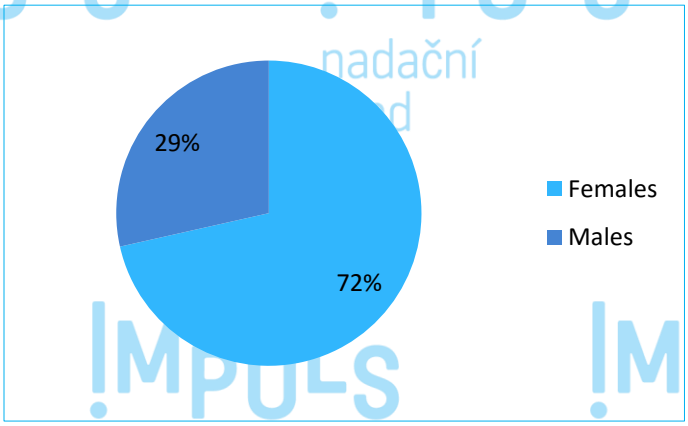

Figure 3 Patient distribution by sex

2.1.2 Age at last patient visit

Mean age at last visit is 41,0 years. For females, mean age was slightly higher than in men. Overall, the registry now includes 33 patients younger than 18 years, and 7 of these are younger than 15 years. When all MS treatment centres are taken together the most represented age group is that of patients aged 30 – 40 years.

Table 4 Patient age in years at last visit

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	41,0	40,4	9,8	78,4	10,3	0

Table 5 Patient age in years at last visit by sex

Centre	Sex	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	Females	41,3	40,9	10,1	74,6	10,4	0
	Males	40,3	39,5	9,8	78,4	10,0	0

Table 6 Number of patients younger than 15 and 18 let, respectively

Age	All centres	
	Number	Percentage
< 15 years	7	0,1%
< 18 years	33	0,4%

Table 7 Number of patients in individual groups by decades

Age	All centres	
	Number	Percentage
0 – 10	1	0,0%
10 – 20	72	0,9%
20 – 30	1175	14,1%
30 – 40	2758	33,0%
40 – 50	2646	31,7%
50 – 60	1351	16,2%
60 – 70	333	4,0%
70 – 80	17	0,2%
80 – 90	0	0,0%
90 – 100	0	0,0%

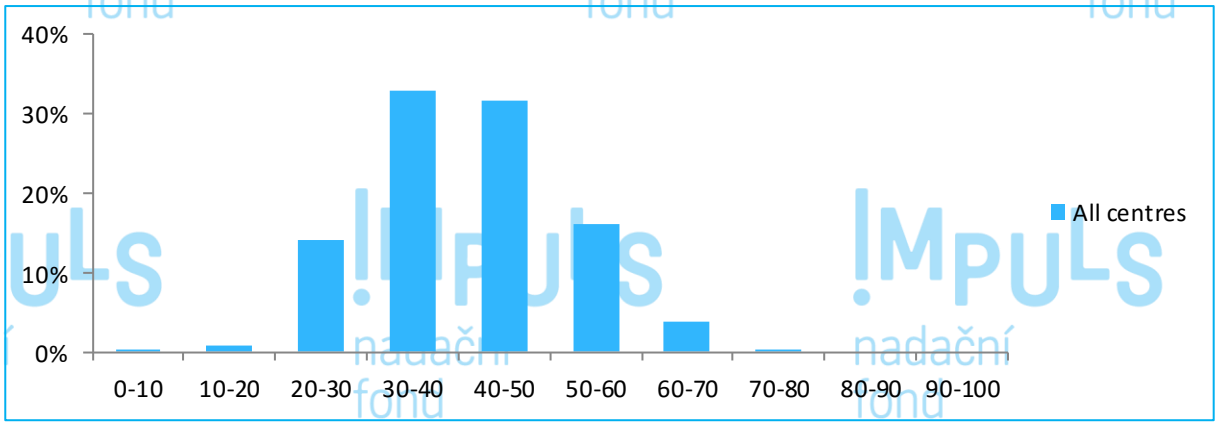

Figure 4 Patient distribution by age

2.1.3 Age at disease onset

Date of disease onset is an important parameter that is used to calculate patient age at disease onset and disease duration period. This parameter was missing for 11 patients.

Mean age at disease onset is 30,6 years. Table 8 shows, however, that patient age at disease onset ranged from 3 years to 67 years.

Table 8 Patient age in years at the time of disease onset

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	30,6	29,4	3,3	67,3	9,6	11

2.1.4 Patient distribution by individual healthcare insurance companies

Table 9 and Figure 5 show the distribution of patients in the registry by individual health insurance companies. 58,1 % patients are insured with the General Health Insurance Company (code: 111). 13,2 % are insured with Health Insurance Company of the Ministry of Internal Affairs (code: 211) and 9,9 % with Business Health Insurance Company (code: 207).

Table 9 Patient distribution by health insurance companies

Health Insurance Co.	All centres	
	Number	Percentage
111	4849	58,1%
201	470	5,6%
205	751	9,0%
207	824	9,9%
209	133	1,6%
211	1103	13,2%
213	219	2,6%
Other	4	0,0%

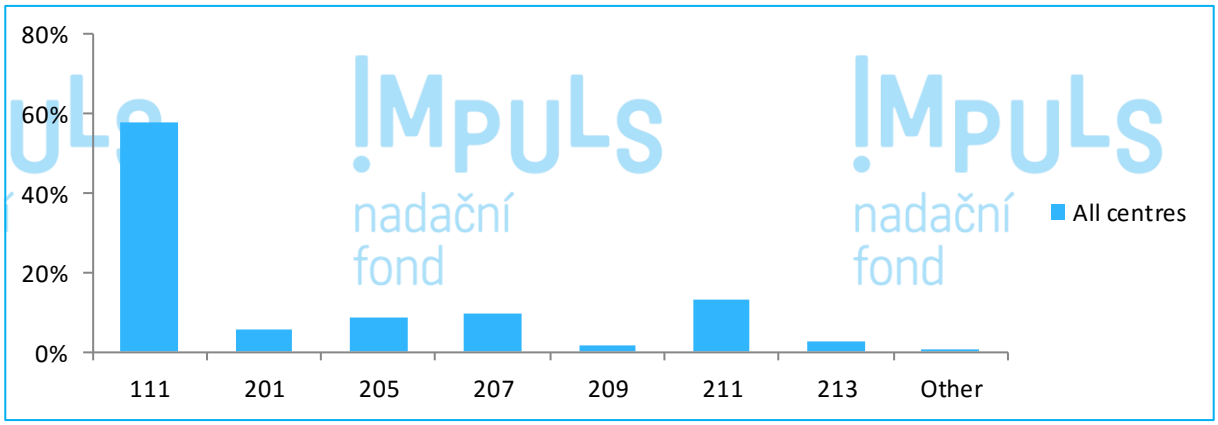

Figure 5 Patient distribution by health insurance companies

2.1.5 Patient distribution by regions

The registry makes it possible to obtain data on patient distribution by individual Czech Republic regions based on ZIP codes attached to patient residence addresses. ZIP codes assigned to communities that were part of two regions were assigned to the region that included most of the included communities. ZIP codes not found in the ZIP code registry of the Czech National Postal Office (Czech Post) were interpreted as incorrect.

The registry includes patients from all Czech Republic regions.

Table 10 Patient distribution by regions of their residence

Regions	All centres	
	Number	Percentage*
South Bohemia	551	6,6%
South Moravia	320	3,8%
Karlovy Vary	227	2,7%
Vysočina	461	5,5%
Hradec Králové	586	7,0%
Liberec	378	4,5%
Moravia-Silesia	788	9,4%
Olomouc	177	2,1%
Pardubice	549	6,6%
Plzeň	419	5,0%
Prague	1644	19,7%
Central Bohemia	1380	16,5%
Ústí nad Labem	687	8,2%
Zlín	182	2,2%

* 1 patient did not have completed residence addresses, 2 patients had the place of permanent residence in Slovakia and 1 patient in Poland

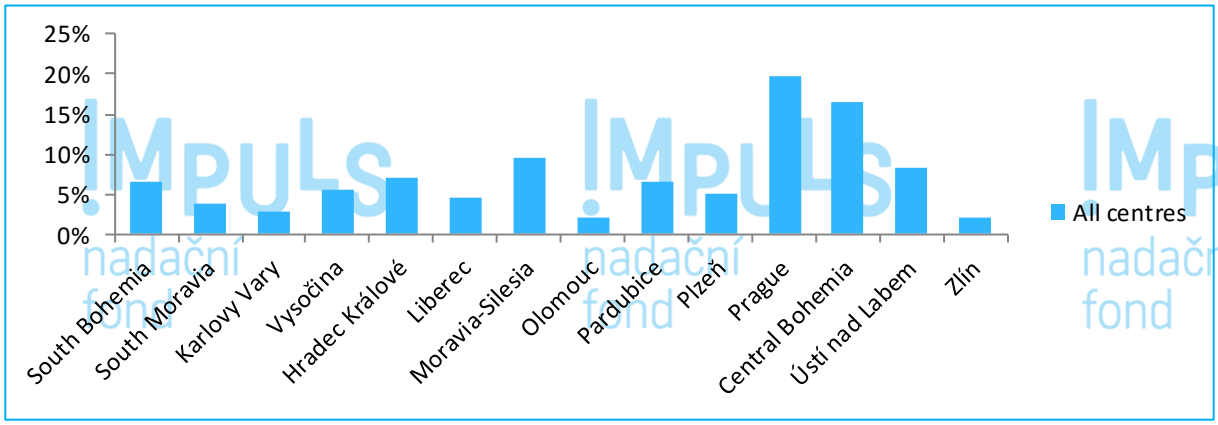

Figure 6 Patient distribution regions of their place of residence

2.2 Employment and social benefits

Employment and provision of social benefits are evaluated based on data obtained at last visit. These parameters must be completed at each visit even when the condition remains the same.

It should be noted that all possibilities and combinations of employment and especially those for social benefits cannot be appreciated and the clarity and purposefulness of the output is preserved at the same time. It was thus necessary to introduce certain preference criteria so the physicians be able to complete the data and decide what options to choose in unclear combined cases. These preference criteria (that is that the type of disability pension [DP] takes precedence over unemployment benefits or maternal leave [ML]) must be taken into account when interpreting and presenting this type of data.

2.2.1 Employment

As part of entering employment data, selection must be made among the options PTE – part-time employment, FTE – full-time employment, DNW – does not work (irrespective of the reasons for employment/unemployment and possible social benefits) and STUDENT – studies (social and health insurance is paid for by the state).

Almost one half of the patients have full-time employment (56,2 %), followed by 13,4 % patients who work part-time.

Table 11 Patient distribution by employment

Employment	All centres	
	Number	Percentage*
PTE	1120	13,4%
FTE	4695	56,2%
DNW	1985	23,8%
STUDENT	237	2,8%

* 3,8 % patients did not have data on employment completed

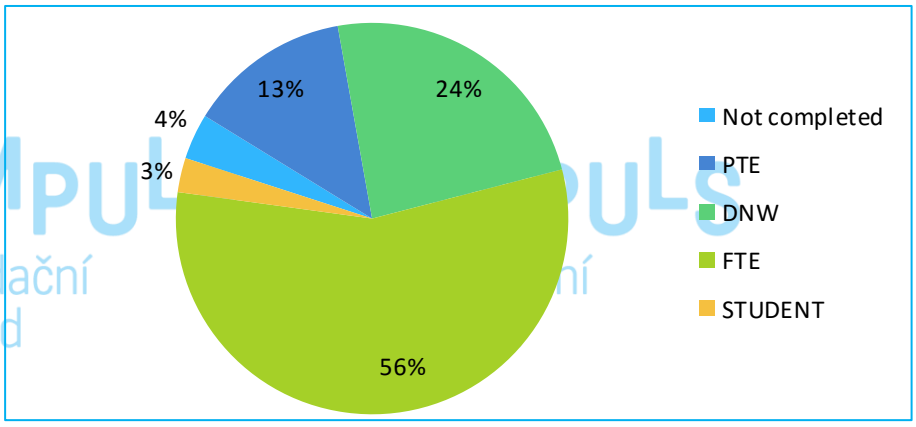

Figure 7 Patient distribution by employment type

2.2.2 Social benefits

The structure of social benefits is based on simplified data as the completer had always to choose one, "most important" benefit in cases where a patient was receiving more benefits. DP1, DP2 and DP3 are social benefits that were of most interest to us - these codes denote 3 degrees of disability pension. ML – maternity leave is only reported as secondary information, as are unemployment benefits (UNEMPL). OAP codes for old-age pension.

55,3 % patients do not receive any social benefit.

Table 12 Patient distribution by type of social benefit

Social benefit	All centres	
	Number	Percentage*
DP1	1094	13,1%
DP2	634	7,6%
DP3	963	11,5%
ML	495	5,9%
UNEMPL	67	0,8%
OAP	167	2,0%
Does not receive (X)	4616	55,3%

* 3,8 % patients had no data completed for social benefits

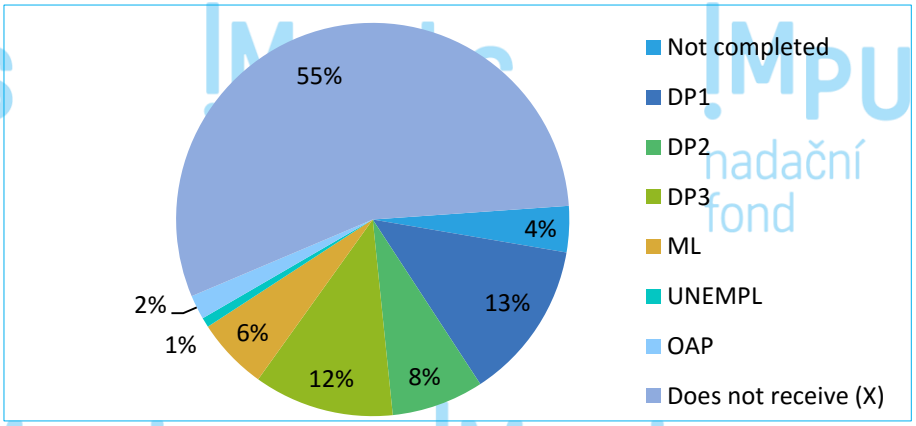

Figure 8 Patient distribution by type of social benefit

2.3 Disease duration period

Mean disease duration period is 10,4 years.

Table 13 Disease duration period (from disease onset to last visit)

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	10,4	8,9	0,1	45,9	7,6	11

2.4 Degree of damage

Degree of damage is assessed using assigned EDSS (Expanded Disability Status Scale) value at each visit. Degree of damage is analysed as that found at the last available patient visit.

EDSS ranges from 0 to 10, where 0 means healthy patient without complaints, degree 5 corresponds to considerable damage, inability to work and ability to walk for a distance less than 500 metres, and degree 10 means death due to MS.

Median EDSS value is 2,5. Most patients are in the EDSS group between 1,5 – 2.

Table 14 Degree of damage (EDSS value) at last visit

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	2,7	2,5	0,0	8,0	1,5	11

Table 15 Degree of damage (EDSS value) at last visit

EDSS	All centres	
	Number	Percentage*
0 – 1	1149	13,8%
1,5 – 2	2983	35,7%
2,5 – 3	1483	17,8%
3,5 – 4	1249	15,0%
4,5 – 5	796	9,5%
5,5 – 6	478	5,7%
6,5 – 7	189	2,3%
7,5 – 8	15	0,2%
8,5 – 9	0	0,0%
9,5 – 10	0	0,0%

* 0,1 % patients had no data completed about EDSS degree

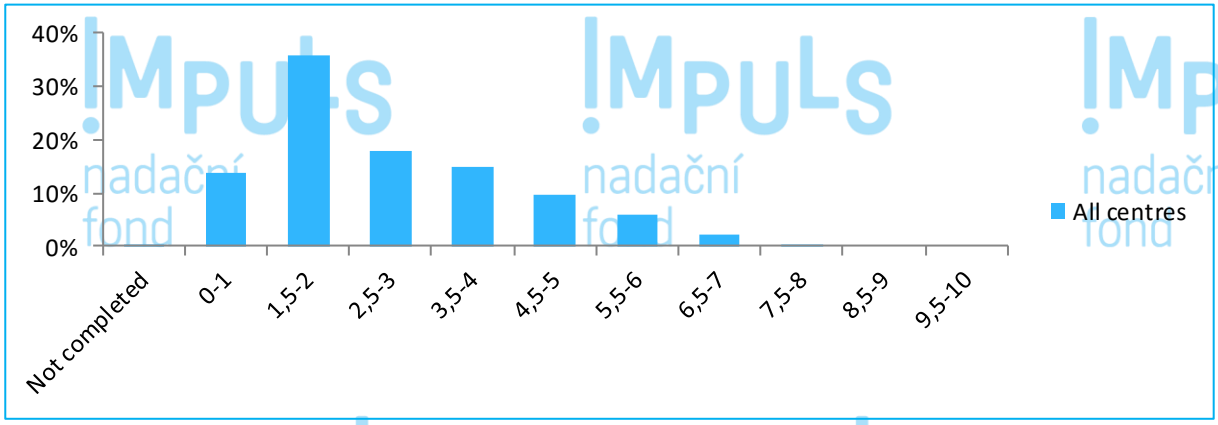

Figure 9 Patient distribution by EDSS degree

2.5 Relapse

Over the last 6 months, relapse of the disease (recurrence of symptoms) was recorded in 10,1 % patients, while this rate was 23,2 % over the period of 12 months. What should be taken into account is that the number of relapses reported here is an overall number including multiple relapses in one patient. Mean number of relapses annually (ARR, annualized relapse rate) is 0,232.

Table 16 Relapse occurrence over last 6 and 12 months

Relapse	All centres	
	Number	Percentage
Over 6 months	846	10,1%
Over 12 months	1938	23,2%

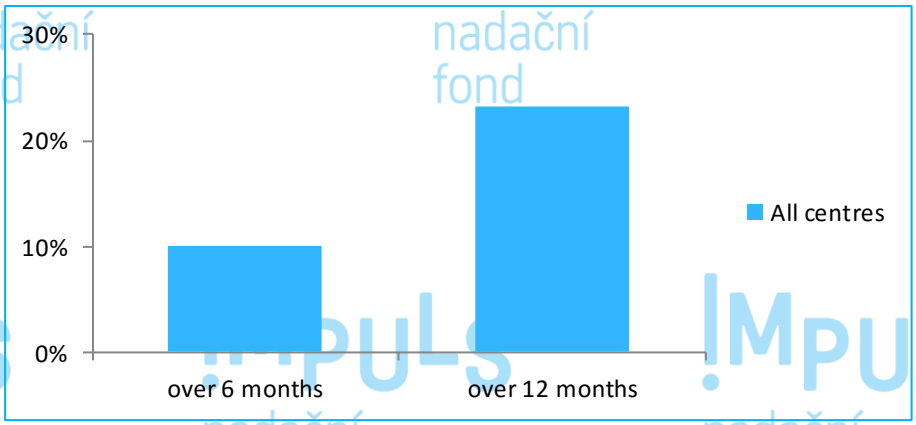

Figure 10 Proportion of relapses over last 6 and 12 months

Relapse severity is defined as mild, moderate or severe. Mild relapse intensity means that the relapse does not impact negatively on activities of daily life (ADLs). Moderate intensity does impact on activities of daily life already, while the severe form is recorded in cases where the relapse is associated with severe discomfort of the patients, deteriorates their activities of daily life significantly and results in their inability to work, or hospital admission.

Severity of most relapses was mild or moderate. Mild relapses accounted for 44,4 % and moderately severe relapses for 51,9 % over the last 6 months. Severe relapses had recorded for 3,5 % over the period of interest.

Table 17 Relapse severity over last 6 and 12 months

Relapse over 6 months	All centres	
	Number	Percentage*
Mild	376	44,4%
Moderate	439	51,9%
Severe	30	3,5%
Relapse over 12 months	**Number**	**Percentage***
Mild	882	45,5%
Moderate	969	50,0%
Severe	85	4,4%

* In 0,1 % of the recorded relapses data on relapse severity over last 6 months were missing
In 0,1 % of the recorded relapses data on relapse severity over last 12 months were missing

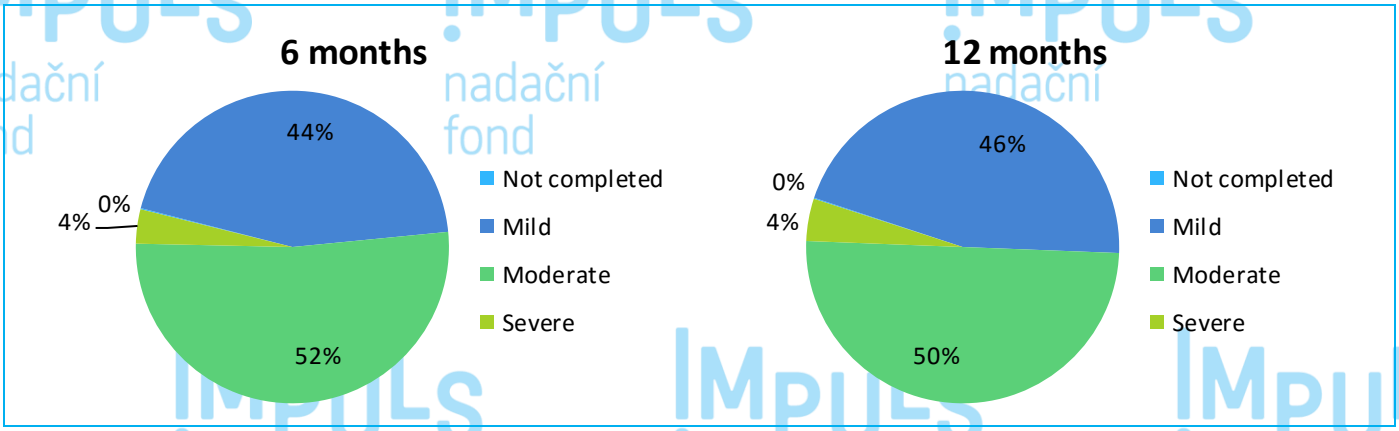

Figure 11 Relapse severity over last 6 and 12 months

The last analysed parameter was the form of relapse treatment – outpatient vs. inpatient treatment. Vast majority of the relapses was treated on outpatient basis. The number of hospitalizations is up to10 percent.

Table 18 Type/form of relapse treatment over last 6 and 12 months

Relapse over 6 months	All centres	
	Number	Percentage*
Outpatient	758	89,6%
Hospital stay	73	8,6%
Relapse over 12 months	**All centres**	
	Number	Percentage*
Outpatient	1704	87,9%
Hospital stay	183	9,4%

* 1,8 % of relapses recorded over the last 6 months data on type of treatment were missing
2,6 % of relapses recorded over the last 12 months data on type of treatment were missing

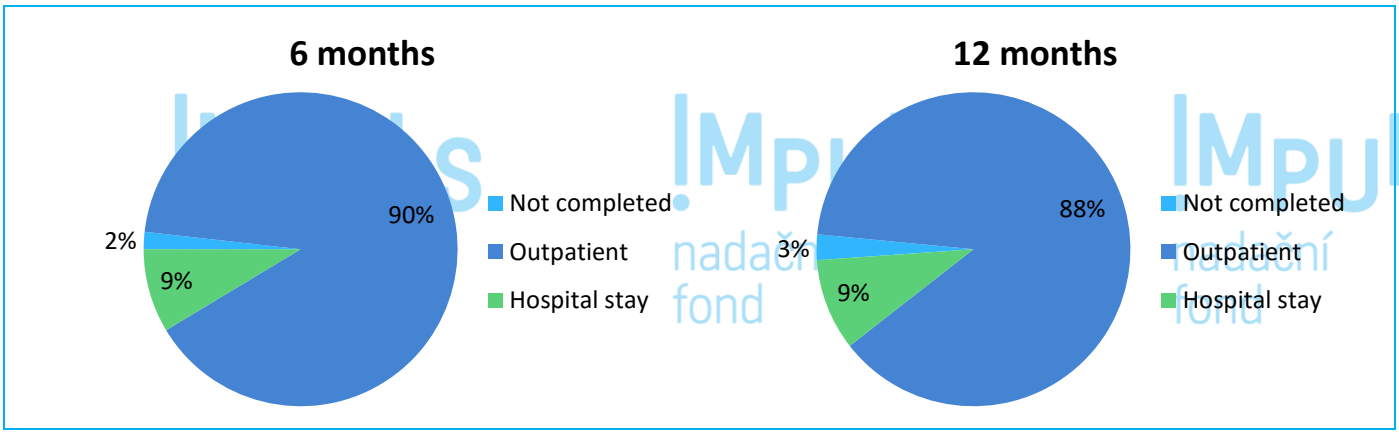

Figure 12 Type/form of treatment over last 6 and 12 months

2.6 Treatment

Evaluation of MS treatment included the preparation used at last visit, a DMD or IVIG. 13 patients did not terminate their treatment for 2 preparations, so the numbers for these patients are included twice. In some cases, it is a parallel treatment with two medicines. It is, however, mostly due to erroneous input into the system (these duplicities will be removed from the registry in the future).

Patients receiving IVIG preparations were included by very few centres in this phase. Some centres still have not specified the concrete type of IVIG. 446 patients (5,3 %) did not receive any DMD or IVIG preparation at their last visit (their treatment was temporarily or permanently discontinued). These 446 patients are not included in Table 19, but are included in Table 20.

Most patients received Copaxone (22,3 %), Rebif (18,8%) and Avonex (17,5 %). 24,0 % of patients was on the escalation therapy at last visit (Gilenya, Lemtrada, Tecfidera, Tysabri).

Table 19 Patient distribution by the preparation used at last visit

Treatment	All centres	
	Number	Percentage
DMD		
Aubagio	302	3,8%
Avonex	1389	17,5%
Betaferon	749	9,5%
Copaxone [20] / [40]	1766	22,3%
Extavia	162	2,0%
Gilenya	744	9,4%
Lemtrada*	12	0,2%
Rebif[22]	570	7,2%
Rebif[44]	915	11,6%
Tecfidera	404	5,1%
Tysabri	736	9,3%
IVIG	1	0,0%
Endobulin	0	0,0%
Flebogamma	96	1,2%
Gammagard	6	0,1%
Kiovig	54	0,7%
Octagam	14	0,2%

* Only patients who were infused Lemtrada at last visit

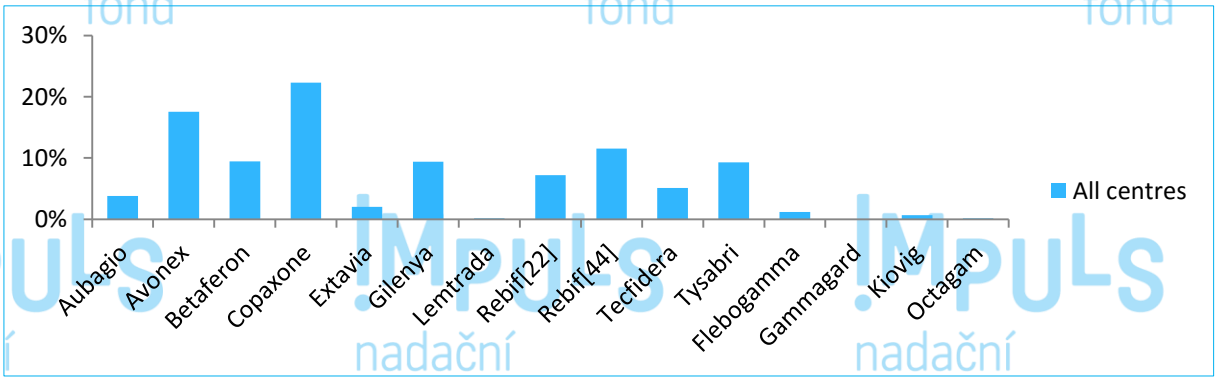

Figure 13 Medicinal preparations used - DMDs and IVIGs

2.6.1 New initiations, terminations or change of therapy with DMDs/ IVIGs

As part of a more detailed analysis of patient treatment the proportion of patients was determined who initiated treatment with new DMD/ IVIG preparations over the last half year prior to data export on 30. 6. 2016. 3,3 % patients initiated treatment with these preparations.

The number of patients who terminated treatment with DMDs over the period of interest cannot be exactly determined at present. At their last visit, 446 patients (5,3 %) received no treatment. 136 (1,6 %) of these patients terminated/discontinued treatment over the half year of interest, and the remaining 310 patients (3,7 %) had terminated treatment earlier and did not initiate new treatment over the period of interest.

The last recorded parameter was the number of patients who changed their DMD or IVIG preparation over the period of interest. The proportion of these patients was 5,0 % overall.

Table 20 Number of patients who initiated new treatment with DMDs/ IVIGs, terminated or changed these preparations over the period of interest

Treatment	All centres	
	Number	Percentage
Initiation	278	3,3%
New termination	136	1,6%
Earlier termination	310	3,7%
Termination overall	446	5,3%
Change	417	5,0%

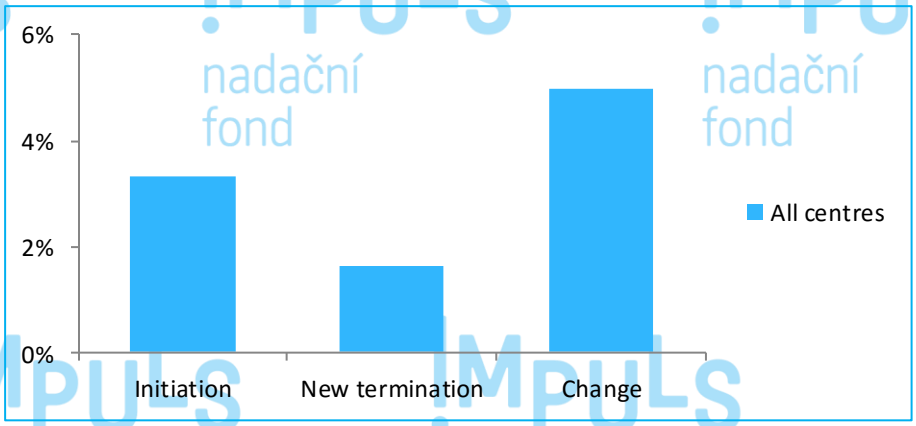

Figure 14 New initiation, termination or change of therapy with DMDs/ IVIGs

2.7 Health-related events

2.7.1 Pregnancy

Over the evaluated period from 1. 1. 2016 to 30. 6. 2016 a total of 51 MS patients (0,9 %) delivered children. 48 of these gave birth to 1 child, 1 patient gave birth to twins and 1 patient gave birth to triplets. For 1 patient number of delivered children was missing.

Table 21 Number of delivered children born over the period of interest

Pregnancies	All centres	
	Number	Percentage
Number of deliveries	51	0,9%

2.7.2 Adverse events

The number of predefined adverse events was equal to 0,4 %. Some centres had not yet started to complete this parameter in more detail. These results cannot thus be reliably interpreted so far. There is no correction in place for data expression in percentages for the case of multiple AEs in one patient.

In the last 6 months, there was reported a suspicion of one severe health-related event, specifically Rebif [44]. It was a necrosis at the site of injection. This adverse event was reported to SÚKL (State Institute for Drug Control).

Table 22 Number of adverse events with first occurrence in the period of interest

Number of adverse events	All centres	
	Number	Percentage
Number of AEs	96	1,1%
Number of predefined AEs	32	0,4%
Number of severe AEs	1	0,0%

3 Conclusion

On 30. 6. 2016, the seventh data export into ReMuS registry was delivered, followed by interim data analysis from the registry focusing on the period from 1. 1. 2016 to 30. 6. 2016. Over the evaluated period data from fourteen MS treatment centres – General University Hospital in Prague (VFN), Hospital in Teplice, Hospital in Jihlava, University Hospital Motol in Prague, University Hospital in Plzeň, Hospital of Pardubice Region, University Hospital in Ostrava, University Hospital Královské Vinohrady in Prague, Thomayer University Hospital Krč in Prague, University Hospital in Hradec Králové, University Hospital in Brno (Bohunice), University Hospital in Olomouc, Hospital in České Budějovice and Regional Hospital T. Baťa in Zlín.These centres enter data on their patients in the registry on continual basis, and as of the day of data export on 30. 6. 2016 data on treatment of 8 585 patients was available. After elimination of patients without actual data, data of 8 353 patients from the whole Czech Republic entered into the analysis.

Of patients included in the registry, 71,5 % are women, mean patient age at last visit is 41,0 years and mean age at disease onset is 30,6 years. 99,6 % patients were older than 18 years at last visit. 58,1 % patients are insured with the General Health Insurance Company. The registry already includes data of patients from all regions of the Czech Republic. 69,6 % patients are able to work (they work full-time or part-time) and 32,2 % receive degree 1-3 disability pensions. The most represented group in terms of degree of damage are patients with EDSS between 1,5 and 2. Mean number of relapses in one year (ARR, annualized relapse rate) is 0,232. More than a half of (51,9 %) relapses over the last 6 months were of moderate severity, and the vast majority of patients were treated as outpatients (89,6%). Medicinal preparations used most commonly are Copaxone (22,3 %), Rebif (18,8 %) and Avonex (17,5 %). 24% of patients was on the escalation therapy at last visit. In the study period, 3,3 % of patients started with DMD treatment, 1,6 % patients ended or interrupted the DMD treatment and 5,0 % of patients changed DMD treatment. A total of 51 MS patients (0,9 %) delivered children during last 6 months. A suspicion of one severe adverse event related to MS treatment (drug: Rebif [44]) was recorded over the evaluated period. This event was reported to SÚKL (State Institute for Drug Control).

Data interpretation should consider that individual MS treatment centres started their participation gradually and added new patients slowly. All participating centres complete and correct data based on error reports.

Compared to the first data export in June 2013, the number of patients in the registry increased more than five-fold while the number of missing data was reduced and with participation of new centres increased variability of patients and their treatment in the Czech Republic.

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