Regular Output from ReMuS Registry

Data export updated on 30. 6. 2014

– Summary Report

In Prague, 21st August 2014

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.

2 Results

As of 30. 6. 2014, ReMuS registry included data of patients from twelve MS treatment centres – General University Hospital in Prague (VFN), Teplice, Jihlava, University Hospital Motol in Prague, University Hospitals in Plzeň, Pardubice, University Hospital in Ostrava, University Hospital Královské Vinohrady, Thomayer University Hospital in Krč, University Hospital in Hradec Králové, University Hospital in Brno (Bohunice), and University Hospital in Olomouc. 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:

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

Table 1 gives the final number of patients included in ReMuS registry as of 30. 6. 2014.

Table 1 Total number of patients by centres

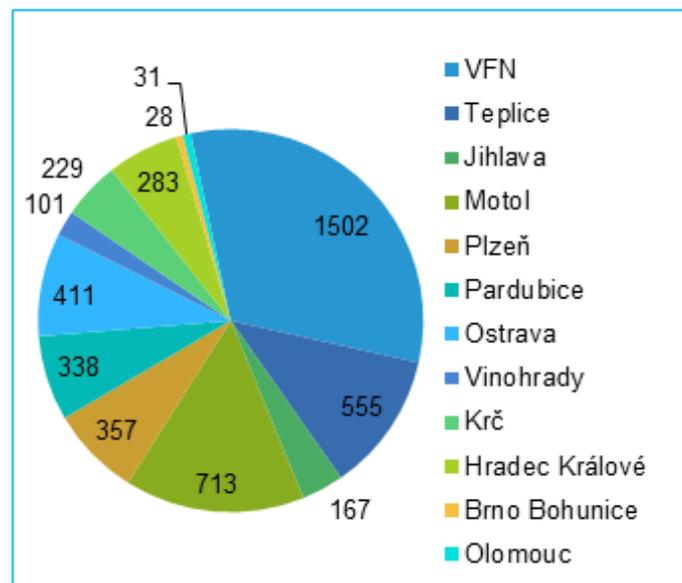| Centre	Number of patients	Percentage
VFN	1502	31,9%
Teplice	555	11,8%
Jihlava	167	3,5%
Motol	713	15,1%
Plzeň	357	7,6%
Pardubice	338	7,2%
Ostrava	411	8,7%
Vinohrady	101	2,1%
Krč	229	4,9%
Hradec Králové	283	6,0%
Brno Bohunice	28	0,6%
Olomouc	31	0,7%
Total	4715	100,0%

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. One year later, in summer 2014, the registry has expanded to include 12 MS treatment centres already, so the data of 4 715 patients from the whole of the Czech Republic enter analysis.

Table 2 Number of patients in the ReMuS registry - development

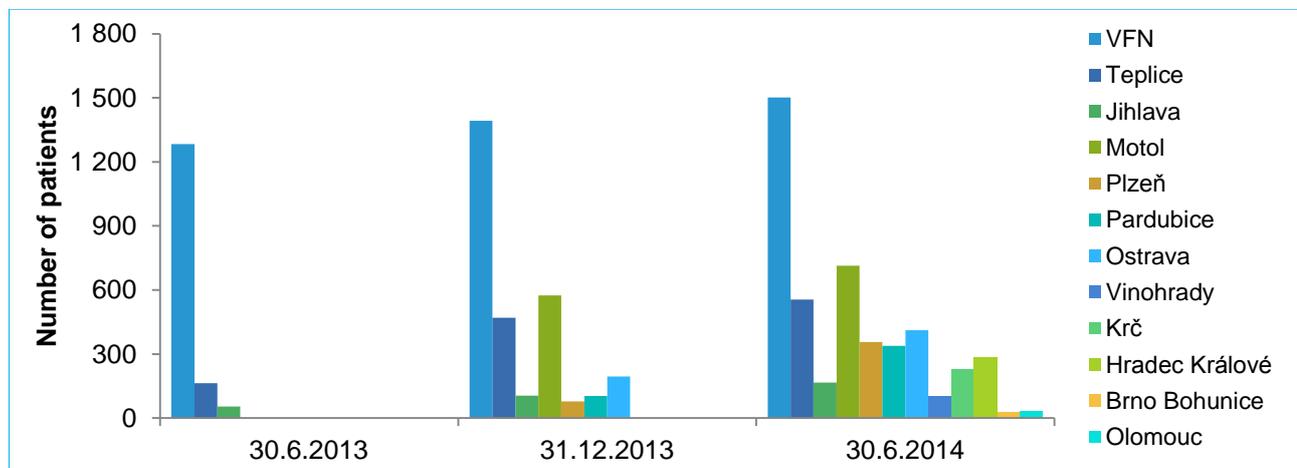| Data export date	Number of centres	Number of patients to be analysed
30.6.2013	3	1501
31.12.2013	7	2920
30.6.2014	12	4715

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 71,6% women and 28,4% men.

Table 3 Patient distribution by sex

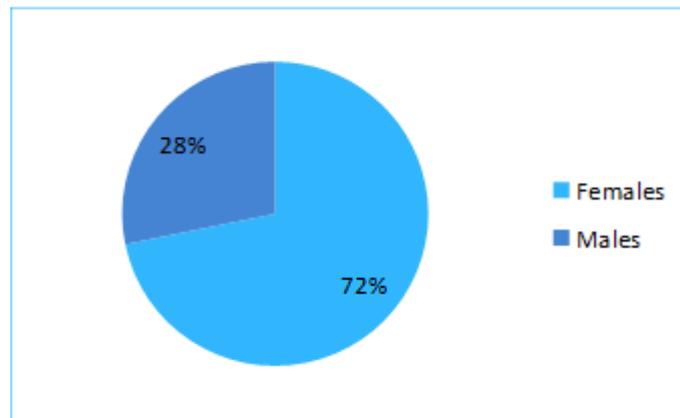| Sex	All centres	
	Number	Percentage
Females	3375	71,6%
Males	1340	28,4%

Figure 3 Patient distribution by sex

2.1.2 Age at last patient visit

Mean age at last visit is 39,9 years. For females, mean age was slightly higher than in men. Overall, the registry now includes 18 patients younger than 18 years, and 2 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	39,9	39,2	13,8	76,6	10,2	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	40,3	39,6	14,0	72,8	10,3	0
	Males	39,0	38,2	13,8	76,6	9,9	0

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

Age	All centres	
	Number	Percentage
< 15 years	2	0,0%
< 18 years	18	0,4%

Table 7 Number of patients in individual groups by decades

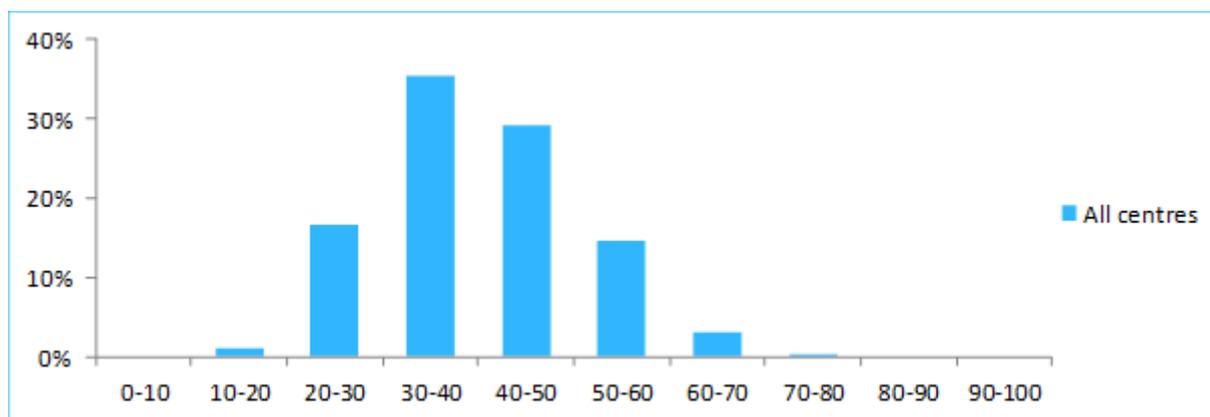| Age	All centres	
	Number	Percentage
0 – 10	0	0,0%
10 – 20	47	1,0%
20 – 30	786	16,7%
30 – 40	1668	35,4%
40 – 50	1374	29,1%
50 – 60	688	14,6%
60 – 70	148	3,1%
70 – 80	4	0,1%
80 – 90	0	0,0%
90 – 100	0	0,0%

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 65 patients.

Mean age at disease onset is 30 years. Table 8 shows, however, that patient age at disease onset ranged from below 4 years to almost 70 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	30,0	28,7	3,5	68,1	9,4	65

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. 59,4% patients are insured with the General Health Insurance Company (code: 111). 12,6% are insured with Health Insurance Company of the Ministry of Internal Affairs (code: 211) and 10,6% with Business Health nsurance Company (code: 207).

Table 9 Patient distribution by health insurance companies

Health Insurance Co.	All centres	
	Number	Percentage*
111	2802	59,4%
201	240	5,1%
205	324	6,9%
207	502	10,6%
209	72	1,5%
211	596	12,6%
213	108	2,3%
217	65	1,4%
Other	2	0,0%

* 0,1 % patients had no data entered for health insurance company
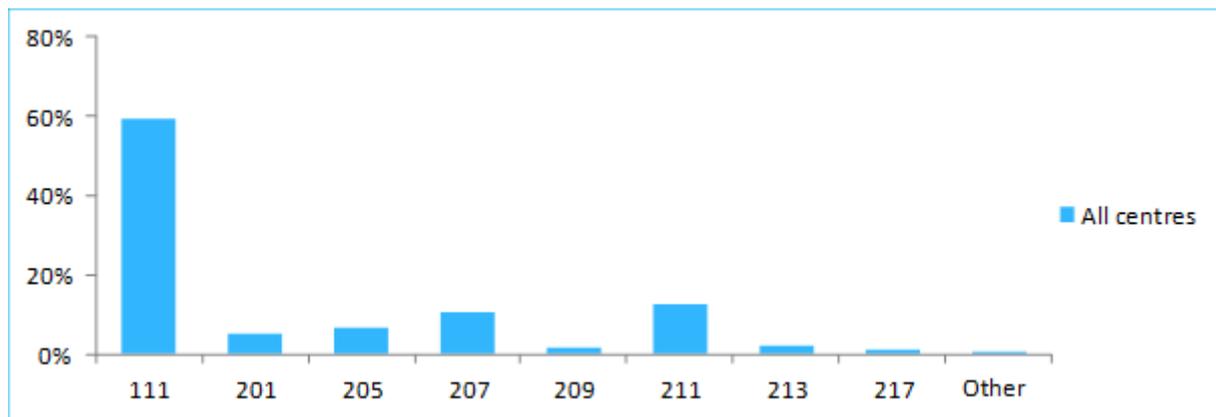

Figure 5 Patient distribution by health insurance companies

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. Low patient numbers from South Moravia and Olomouc regions are due to slow participation initiation of MS treatment centres in Brno and Olomouc. Patient data are gradually completed in the registry and will be part of the winter data export in December 2014.

Table 10 Patient distribution by regions of their residence

Regions	All centres	
	Number	Percentage*
South Bohemia	127	2,7%
South Moravia	66	1,4%
Karlovy Vary	153	3,2%
Vysočina	265	5,6%
Hradec Králové	243	5,2%
Liberec	224	4,8%
Moravia-Silesia	378	8,0%
Olomouc	48	1,0%
Pardubice	365	7,7%
Plzeň	311	6,6%
Prague	1065	22,6%
Central Bohemia	895	19,0%
Ústí nad Labem	457	9,7%
Zlín	60	1,3%

* 1,2 % patients did not have correctly completed ZIP code
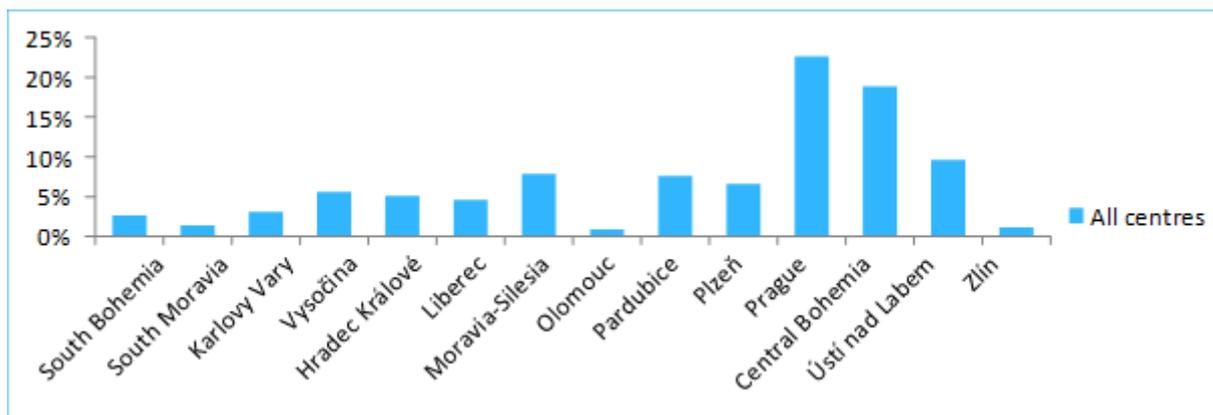

Figure 6 Patient distribution regions of their place of residence

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 (49,3%), followed by 12,6% patients who work part-time.

Table 11 Patient distribution by employment

Employment	All centres	
	Number	Percentage*
PTE	594	12,6%
FTE	2327	49,3%
DNW	1144	24,2%
STUDENT	156	3,3%

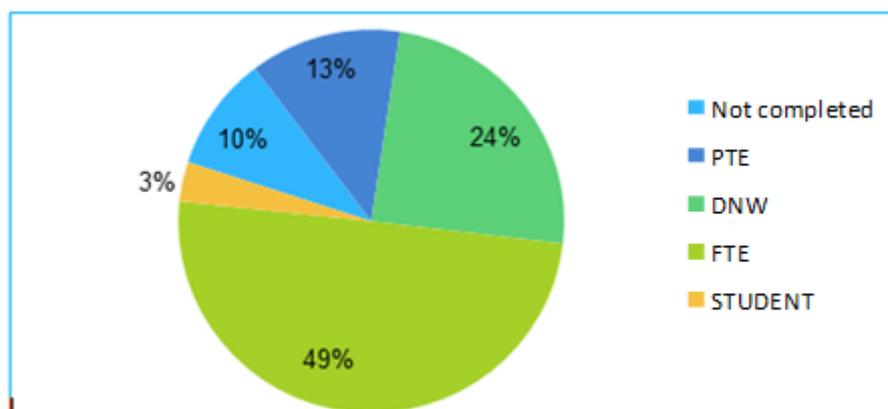* 9,6 % patients did not have data on employment completed

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.

46,1% patients do not receive any social benefit.

Table 12 Patient distribution by type of social benefit

Social benefit	All centres	
	Number	Percentage*
DP1	615	13,0%
DP2	363	7,7%
DP3	573	12,1%
ML	247	5,2%
UNEMPL	73	1,5%
OAP	68	1,4%
Does not receive (X)	2176	46,1%

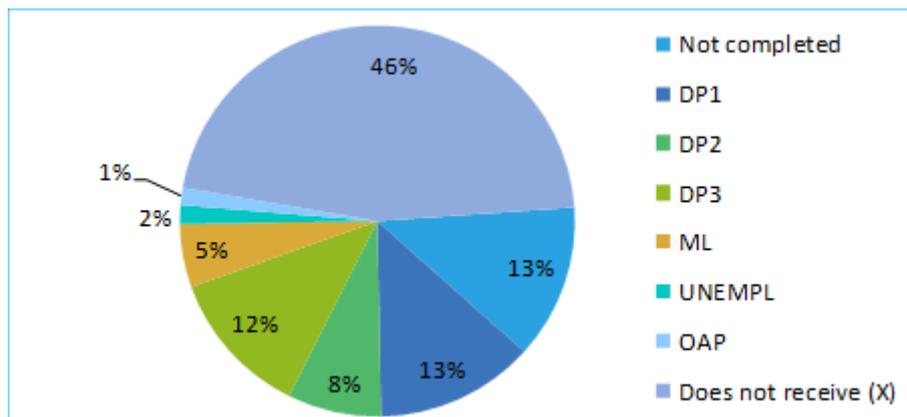* 12,7 % patients had no data completed for social benefits

Figure 8 Patient distribution by type of social benefit

2.3 Disease duration period

Mean disease duration period is 9,9 years.

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

Centre	Mean	Median	Minimum	Maximum	SD	Number of missing values
All centres	9,9	8,2	0,1	43,9	7,4	65

2.4 Degree of damage

Degree of damage is assessed using assigned EDSS (Expanded Disability Status Scale) value at each visit. Similar to all parameters that must be completed at each visit, there were uncompleted values here as well. 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	8,5	1,5	199

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

EDSS	All centres	
	Number	Percentage*
0 – 1	618	13,1%
1,5 – 2	1665	35,2%
2,5 – 3	822	17,4%
3,5 – 4	670	14,2%
4,5 – 5	459	9,7%
5,5 – 6	209	4,4%
6,5 – 7	68	1,4%
7,5 – 8	6	0,1%
8,5 – 9	1	0,0%
9,5 – 10	0	0,0%

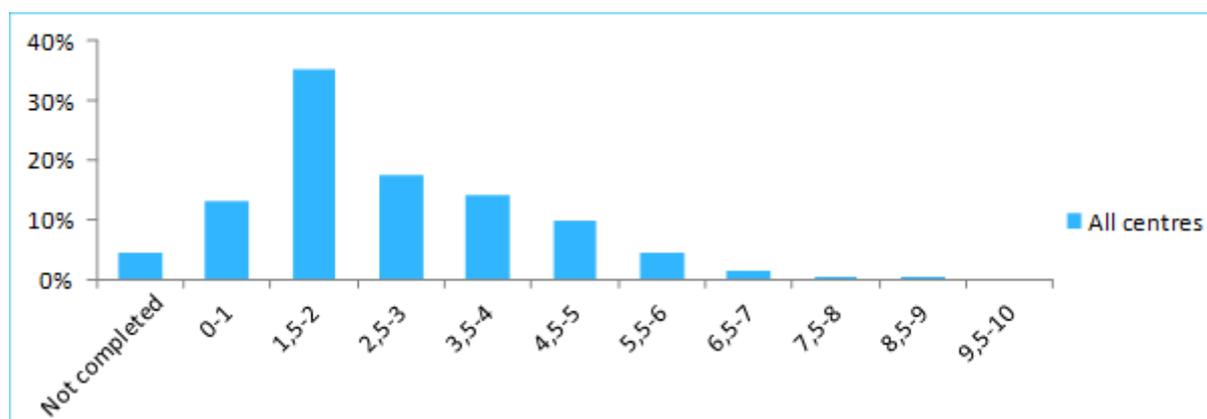* 4,2 % patients had no data completed about EDSS degree

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 11,2% patients, while this rate was 26,0% 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 0,260.

Table 16 Relapse occurrence over last 6 and 12 months

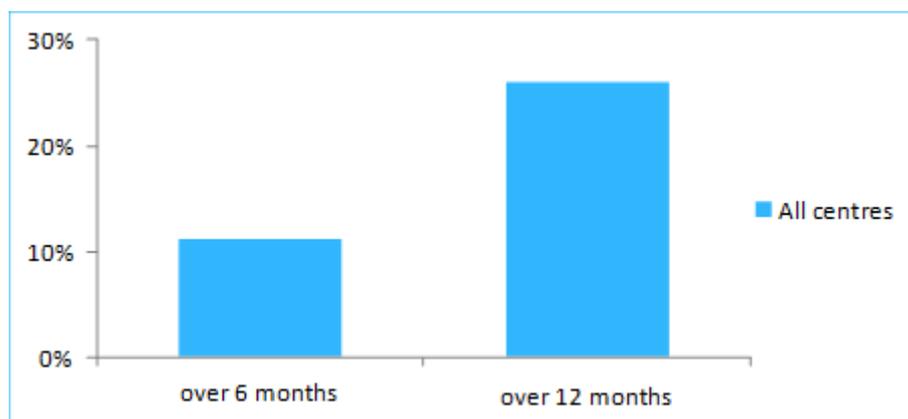| Relapse	All centres	
	Number	Percentage
Over 6 months	526	11,2%
Over 12 months	1227	26,0%

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. Moderate-intensity relapses account for 45,2% of all recorded relapses over the last 6 months.

Table 17 Relapse severity over last 6 and 12 months

Relapse over 6 months	All centres	
	Number	Percentage*
Mild	224	42,6%
Moderate	238	45,2%
Severe	38	7,2%
Relapse over 12 months	Number	Percentage*
Mild	526	42,9%
Moderate	557	45,4%
Severe	79	6,4%

* In 4,9 % of the recorded relapses data on relapse severity over last 6 months were missing
 In 5,3 % of the recorded relapses data on relapse severity over last 12 months were missing
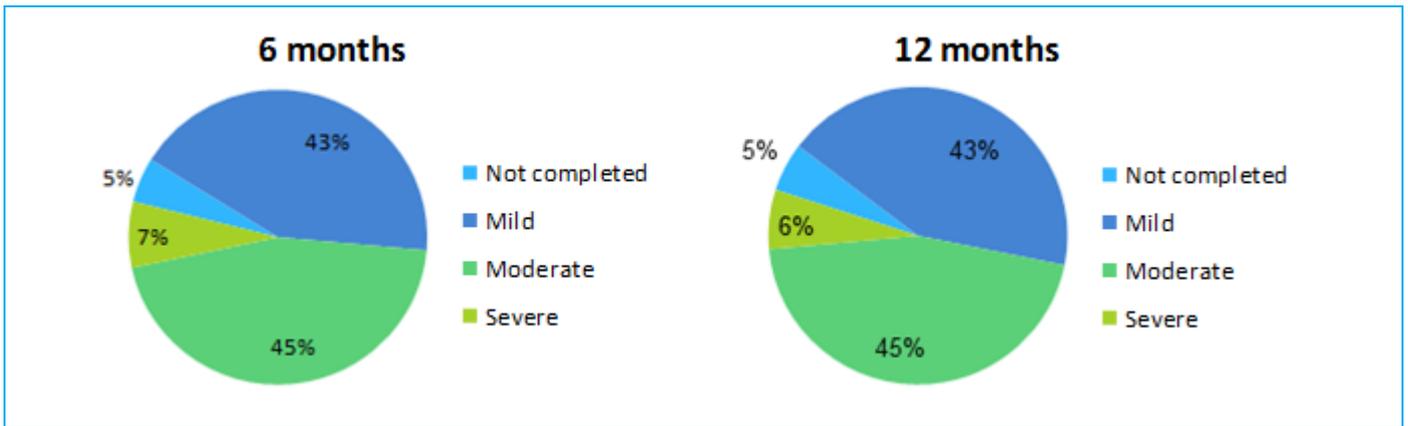
Figure 11 Relapse severity over last 6 and 12 months

The last analysed parameter was the form of relapse treatment – outpatient vs. inpatient treatment. Vast majority of the relapses was treated on outpatient basis. Rates of hospital treatments in individual centres were single-digit.

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

Relapse over 6 months	All centres	
	Number	Percentage*
Outpatient	481	91,4%
Hospital stay	28	5,3%
Relapse over 12 months	All centres	
	Number	Percentage*
Outpatient	1086	88,5%
Hospital stay	102	8,3%

* 3,2 % of relapses recorded over the last 6 months data on type of treatment were missing

   3,2 % of relapses recorded over the last 12 months data on type of treatment were missing
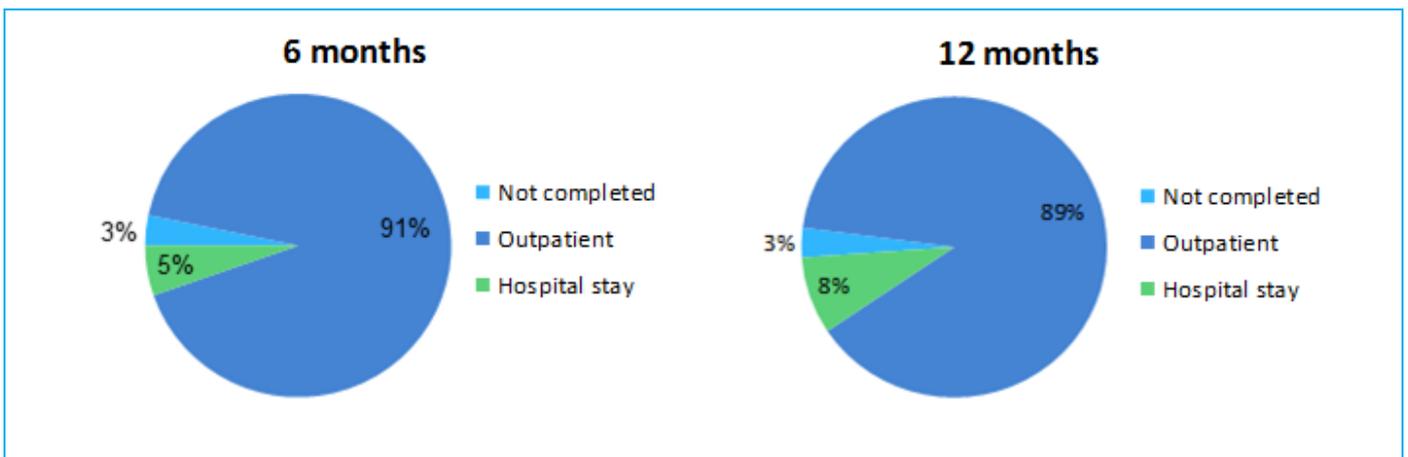

Figure 12 Form of treatment over last 6 and 12 months

2.6 Treatment

Evaluation of MS treatment included the preparation used at last visit, a DMD or IVIG. 8 patients did not terminate their treatment for 2 preparations, so the numbers for these patients are included twice (these duplicities will be removed from the registry in the future).

Patients receiving IVIG preparations were included by very few centres in this phase. 136 patients (2,9 %) did not receive any DMD or IVIG preparation at their last visit (their treatment was temporarily or permanently discontinued). These 136 patients are not included in Table 19, but are included in Table 20.

Most patients received Copaxone (24,4 %) or Avonex (20,8 %).

Table 19 Patient distribution by the preparation used at last visit

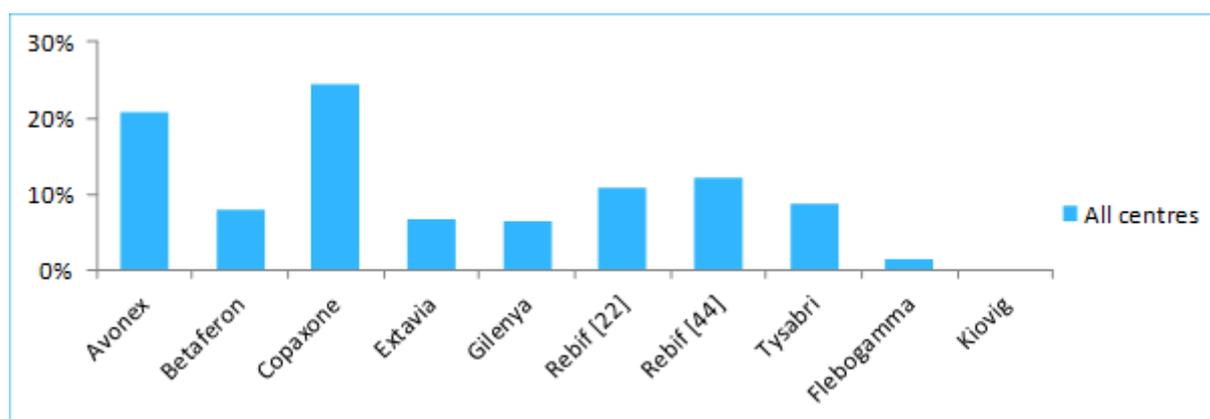| Treatment	All centres	
	Number	Percentage
DMD		
Avonex	956	20,8%
Betaferon	361	7,9%
Copaxone	1121	24,4%
Extavia	309	6,7%
Gilenya	292	6,4%
Rebif[22]	503	11,0%
Rebif[44]	557	12,1%
Tysabri	406	8,9%
IVIG	8	0,2%
Endobulin	0	0,0%
Flebogamma	66	1,4%
Gammagard	0	0,0%
Kiovig	8	0,2%
Octagam	0	0,0%

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 31. 06. 2014. 3,0% 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, 136 patients (2,9%) received no treatment. 58 of these patients terminated/discontinued treatment over the half year of interest, and the remaining 78 patients 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 3,8% overall.

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

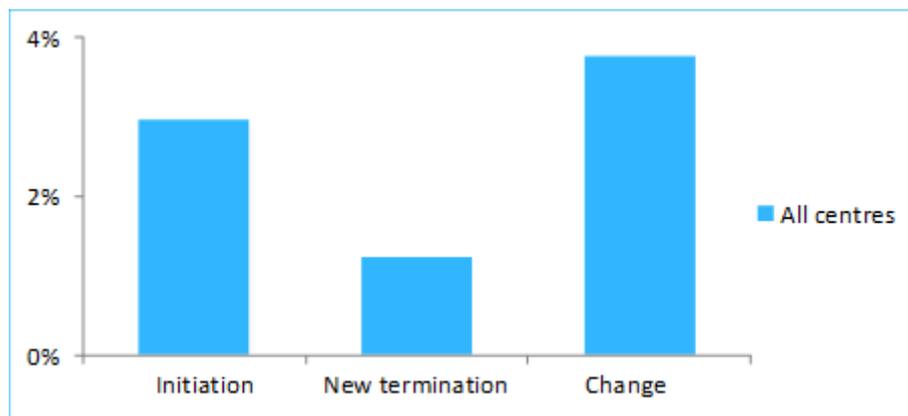| Treatment	All centres	
	Number	Percentage
Initiation	140	3,0%
New termination	58	1,2%
Earlier termination	78	1,7%
Termination overall	136	2,9%
Change	178	3,8%

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

2.7 Health-related events

2.7.1 Pregnancy

Over the evaluated period from 1. 1. 2014 to 31. 12. 2014 a total of 28 MS patients (0,8 %) delivered children. 23 of these gave birth to 1 child, and the remaining 5 patients were found to have no data entered on the number of delivered children.

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

Pregnancies	All centres	
	Number	Percentage
Number of deliveries	28	0,8%

2.7.2 Adverse events

Very few adverse events were recorded. 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.

No severe adverse events relate to the treatment of MS have been recorded over the last 6 months.

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	81	1,7%
Number of predefined AEs	26	0,6%
Number of severe AEs	0	0,0%

3 Conclusion

On 30. 06. 2014, the third data export into ReMuS registry was delivered, followed by interim data analysis from the registry focusing on the period from 1. 1. 2014 to 30. 06. 2014. Over the evaluated period data from twelve MS treatment centres included in ReMuS registry were available - General University Hospital in Prague (VFN), from Teplice, Jihlava, University Hospital in Motol, Prague, Pardubice, University Hospital in Olomouc, University Hospital Královské Vinohrady, Thomayer Hospital in Krč, University Hospital Hradec Králové, University Hospital in Brno (Bohunice), and University Hospital in Olomouc. These centres enter data on their patients in the registry on continual basis, and as of the day of data export on 30. 06. 2014 data on treatment of 4 715 patients was available.

Of patients included in the registry, 71,6 % are women, mean patient age at last visit is 39,9 years and mean age at disease onset is 30,0 years. 99,6 % patients were older than 18 years at last visit. Almost 60 % patients are insured with the General Health Insurance Company. The registry already includes data of patients from all regions of the Czech Republic. There was marked improvement of data quality and percentages of completed data for employment and social benefits. 61,9 % patients are able to work (they work full-time or part-time) and 32,8 % 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 0,260. Almost one half (45,2 %) relapses over the last 6 months were of moderate severity, and the vast majority of patients were treated as outpatients. Medicinal preparations used most commonly are Copaxone (24,4 %) and Avonex (20,8 %). Very few centres entered patients treated with preparations from the IVIG group into the registry. No severe adverse event related to MS treatment occurred over the evaluated period.

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. It is possible to expect growing numbers of patients and improving data quality, mainly in those MS treatment centres that started their participation most recently, in Brno and Olomouc.

Compared to the first data export in June 2013, the number of patients in the registry has now tripled, while the number of both erroneous and missing data could be reduced, and last but not least, participation of new centres has accentuated and deepened patient and treatment variability in the Czech Republic.