

Supplementary Digital Content for

Validation of the Swedish MS register: Further improving a resource for pharmaco- epidemiological evaluations

Alping P, Piehl F, Langer-Gould A, Frisell T, on behalf of the COMBAT-MS Study Group

Supplementary tables:

eTable 1: Contingency tables of contrast-enhancing lesions, expanded disability status scale, infusions, magnetic resonance imaging, and relapses.

eTable 2: Sensitivity, specificity, positive predictive value, and negative predictive value for contrast-enhancing lesions and relapses.

eTable 3: Number of confirmed observations after chart update and percent of the total number of observations before the update, stratified by region.

eTable 4: Number of added observations after chart update and percent of the total number of observations before the update, stratified by region.

eTable 5: Contingency table of EDSS values before and after the update.

eTables 6 and 7: Additional data and results from regression models used to identify the strongest predictors of having pre-update missing data on EDSS and MRI at treatment start.

Supplementary text:

eAppendix 1 - Instructions to clinics: Instructions to clinics detailing the clinical chart review.

eTable 1: Presence of 1+ observations of each variable recorded in register pre-update, compared to observations retrieved from medical charts within 1 to 3 years of therapy start

		Within 1 year			Within 2 years			Within 3 years		
		Not in chart	In chart	All	Not in chart	In chart	All	Not in chart	In chart	All
CEL	Not in register	5114	167	5281	4997	225	5222	4947	253	5200
	In register	9	187	196	10	245	255	10	267	277
	All	5123	354	5477	5007	470	5477	4957	520	5477
EDSS	Not in register	1959	256	2215	1440	240	1680	1330	229	1559
	In register	1	3261	3262	0	3797	3797	0	3918	3918
	All	1960	3517	5477	1440	4037	5477	1330	4147	5477
MRI	Not in register	2728	1023	3751	2003	1236	3239	1828	1257	3085
	In register	3	1723	1726	1	2237	2238	2	2390	2392
	All	2731	2746	5477	2004	3473	5477	1830	3647	5477
Relapse	Not in register	4796	147	4943	4586	194	4780	4497	209	4706
	In register	12	522	534	12	685	697	12	759	771
	All	4808	669	5477	4598	879	5477	4509	968	5477

Notes: CEL=contrast-enhancing lesions, EDSS=expanded disability status scale, MRI=magnetic resonance imaging

eTable 2: Accuracy of having at least one contrast-enhancing lesion and relapse, respectively, by time since treatment start

	Sensitivity	Specificity	PPV	NPV
CEL within 1 year	52.8	99.8	95.4	96.8
CEL within 2 years	52.1	99.8	96.1	95.7
CEL within 3 years	51.3	99.8	96.4	95.1
Relapse within 1 year	78.0	99.8	97.8	97.0
Relapse within 2 years	77.9	99.7	98.3	95.9
Relapse within 3 years	78.4	99.7	98.4	95.6

Notes: PPV=positive predictive value, NPV=negative predictive value, CEL=contrast-enhancing lesions

eTable 3: Number of confirmed observations after chart update in percent of the total number of observations before the update, stratified by region. This corresponds to the second column (“Confirmed”) in Table 1 of the main report

	Therapy (%)	Infusions (%)	Relapse (%)	MRI (%)	EDSS (%)
Skåne	799 (92)	48 (98)	448 (91)	219 (19)	2148 (99)
Stockholm	2148 (92)	1174 (97)	2155 (95)	3002 (69)	6562 (98)
Uppsala	253 (76)	27 (73)	589 (95)	427 (76)	1335 (98)
Västerbotten	231 (86)	686 (96)	273 (99)	681 (75)	1279 (100)
Västra Götaland	1358 (90)	31 (78)	866 (90)	450 (71)	4001 (99)
Örebro	383 (94)	344 (100)	238 (94)	345 (55)	1033 (100)
Östergötland	288 (94)	58 (98)	351 (92)	579 (78)	1066 (100)

Notes: EDSS=expanded disability status scale, MRI=magnetic resonance imaging

eTable 4: Number of added observations after chart update and percent of the total number of observations before the update, stratified by region. This corresponds to fifth column (“Added”) in Table 1 of the main report

	Therapy (%)	Infusions (%)	Relapse (%)	MRI (%)	EDSS (%)
Skåne	33 (4)	95 (194)	414 (84)	1103 (95)	671 (31)
Stockholm	79 (3)	705 (58)	566 (25)	1324 (30)	660 (10)
Uppsala	73 (22)	77 (208)	154 (25)	230 (41)	281 (21)
Västerbotten	31 (11)	66 (9)	27 (10)	97 (11)	16 (1)
Västra Götaland	74 (5)	229 (572)	535 (56)	3234 (512)	693 (17)
Örebro	5 (1)	9 (3)	60 (24)	326 (52)	72 (7)
Östergötland	9 (3)	107 (181)	78 (20)	82 (11)	19 (2)

Notes: EDSS=expanded disability status scale, MRI=magnetic resonance imaging

eTable 5: Contingency table of expanded disability status scale (EDSS) values before and after the update

		EDSS in chart																
		0	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5
EDSS in register	0	3681	19	6	8	1	0	1	0	0	0	0	0	0	0	0	0	0
	1	1	3439	11	21	3	2	0	0	0	0	0	0	0	0	0	0	0
	1.5	0	5	1972	15	3	1	1	0	0	0	0	0	0	0	0	0	0
	2	0	0	5	3174	12	4	1	0	0	0	0	0	0	0	0	0	0
	2.5	0	0	0	2	1460	10	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	2	1	1394	4	1	1	1	0	1	0	0	0	0	0
	3.5	0	0	0	0	0	3	996	10	1	2	0	1	0	0	0	0	0
	4	0	1	0	0	0	1	0	595	0	0	0	1	0	0	0	0	0
	4.5	0	0	0	0	0	0	0	0	167	0	0	0	0	0	0	0	0
	5	0	0	0	0	2	0	0	0	0	145	0	0	0	0	0	0	0
	5.5	0	0	0	0	0	0	0	0	0	0	99	0	0	0	0	0	0
	6	0	0	0	0	0	1	0	0	0	0	0	197	0	0	0	0	0
	6.5	0	0	0	0	0	0	0	0	0	0	0	0	125	0	0	0	0
	7	0	0	0	0	0	0	0	0	0	0	0	0	0	17	0	0	0
	7.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0
	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0
	8.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Regression models

To identify the strongest predictors of having pre-update missing data on EDSS and MRI at treatment start, we used logistic regression models with Akaike information criterion (AIC)-based backward selection among available covariates. To reduce variability, these analyses were run for rituximab, fingolimod, and natalizumab only (the dominant second line therapy options).

The initial models included:

Change in EDSS: Therapy, Number of therapies, Region, Age, Sex, Time since debut, Time since diagnosis

Change in MRI: Therapy, Number of therapies, Region, Age, Sex, Time since debut, Time since diagnosis

The final models after AIC-based backward selection were:

eTable 6: EDSS change, estimated coefficients in final model

	Estimate	Std. Error	z value	p	
Therapy - Rituximab	0.61475	0.23461	2.620	0.008786	**
Therapy - Natalizumab	0.05209	0.22891	0.228	0.820008	
Number of therapies	-0.47479	0.09860	-4.815	1.47e-06	***
Region - Östergötland	-1.16765	0.64182	-1.819	0.068867	.
Region - Skåne	1.21804	0.31631	3.851	0.000118	***
Region - Stockholm	-0.21799	0.28575	-0.763	0.445542	
Region - Uppsala	-0.37440	0.58102	-0.644	0.519323	
Region - Västerbotten	-2.97953	1.03719	-2.873	0.004070	**
Region - Västra Götaland	-0.14588	0.33879	-0.431	0.666759	
Sex - Male	-0.35086	0.18641	-1.882	0.059810	.

Notes: Signif. codes: 0='***', 0.001='**', 0.01='*', 0.05='.', 0.1=' '

eTable 7: MRI change, estimated coefficients in final model

	Estimate	Std. Error	z value	p	
Therapy - Rituximab	-5.019e-02	1.456e-01	-0.345	0.730257	
Therapy - Natalizumab	-3.212e-01	1.370e-01	-2.345	0.019014	*
Region - Östergötland	-1.679e+00	3.998e-01	-4.200	2.67e-05	***
Region - Skåne	3.823e-01	2.103e-01	1.817	0.069165	.
Region - Stockholm	-6.704e-01	1.781e-01	-3.765	0.000166	***
Region - Uppsala	-7.276e-01	3.661e-01	-1.987	0.046873	*
Region - Västerbotten	-2.735e+00	5.313e-01	-5.148	2.63e-07	***
Region - Västra Götaland	2.018e+00	1.992e-01	10.133	< 2e-16	***
Age	2.975e-05	1.427e-05	2.084	0.037159	*

Notes: Signif. codes: 0='***', 0.001='**', 0.01='*', 0.05='.', 0.1=' '

eAppendix 1 - Instructions to clinics

Introduction

COMBAT-MS (COMparison Between All Immunotherapies for Multiple Sclerosis) is an observational, long-term, prospective, cohort study which aims to investigate safety, effectiveness and patient satisfaction of disease-modifying therapies used in relapsing-remitting multiple sclerosis (MS) in Sweden.

Central to the collection of data in COMBAT-MS is the Swedish MS Register (SMSreg). The SMSreg was officially launched in 2001 and has since been an important part in clinical work, as well as MS research.

The COMBAT-MS study is divided into two parts: a retrospective update of data in the SMSreg, followed by a continued prospective data acquisition. It is the retrospective update of the SMSreg that is described here.

Organisation

The coordinating responsible researcher is Fredrik Piehl at the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm. Seven major MS centres will take part in the retrospective update. For participating research heads and contributing researchers, see the last section of this documents.

Method

Patients belonging to the different centres are identified through the SMSreg and lists of these patients are distributed to the research head at the respective centre. Data are then collected through an organized clinical chart review according to a template (see next section) and **registered in SMSreg**. All variables specified in the template are registered from the specified starting point and as far ahead as possible, i.e. until the date of the chart review is performed for the specific patient. Do you have patients in the clinic who meet the Inclusion Criteria but are missing from the list? If so, add them to the SMSreg and enter them on your list.

Important for data collection

For each patient, check the Inclusion Criteria and then fill in any missing data from the clinical chart (according to the collection template) in the MS Register. Avoid making estimates or other personal judgement calls as far as possible. Register data as listed in the clinical chart. The only exception to this is EDSS, which can be assessed from a documented comprehensive neurological examination (see EDSS estimation under clarifications). The therapy that makes the patient available for inclusion in the study (according to Inclusion Criteria, Item 1) is called the ***inclusion therapy*** in this document.

Timetable

- **Start:** Retrospective clinical chart review and registration in the MS register is expected to start mid-February, 2017
- **End:** The retrospective data collection for all patients is to be completed by **1 June, 2017**.

Before you begin

- Read this information
- Get acquainted with the collection template
- Read the paragraphs with clarifications and frequently asked questions
- Contact the contact person for any questions or uncertainties

Follow-up

- It is important to immediately contact the contact person in the case of any uncertainties or other issues
- At the end of each month, the research head or another person responsible for the data collection at each site sends an email to contact person where any uncertainties are listed and the general progress is reported.
- At the beginning of each month an email will be sent to the research head at each site with any clarifications and other information.

Contact

Coordinating responsible researcher

Fredrik Piehl
Neuroimmunology Unit
Dept. Clinical Neuroscience Karolinska Institutet
CMM L08; 04 Karolinska University Hospital (Solna)
S171 76 Stockholm
fredrik.piehl@ki.se
Fax + 46-851773757, Ph + 46-851779840/0000

Web page

This document [the original document in Swedish] is also available at <http://ki.se/meds/combat-ms-retrospektiv-datainsamling>

Template for data collection

1. **Check Inclusion Criteria**
2. **Basic data and disease information**
3. **Therapies (all)**
4. **Relapses**
5. **MRI**
6. **EDSS**
7. **MSIS-29, EQ5D, SDMT, MS-kollen, FSMC, TSQ**
8. **Register the patient as a participant in the study (“Retro_COMBAT-MS”)**

Check inclusion criteria (see Inclusion Criteria Paragraph)

Cancel the review and do not register “Retro_COMBAT-MS”, if the patient does not meet the criteria

1. Identify inclusion therapy, i.e. the first disease modifying therapy¹ commenced after 2011-01-01
2. Check maximum of 1 disease-modifying therapy before the inclusion therapy²
3. Check CIS/Relapsing-remitting MS at start of therapy, NOT primary or secondary progressive MS

Basic data and disease information

- Estimated disease debut and diagnosis date
- Progress type and, if possible, conversion year to SPMS

Therapies

- **All**
- Start date
- Date of completion, and reasons for completion
- If Mabthera, Lemtrada or MabCampath:
 - All infusion dates and doses (may be recorded in the nurse’s charts)
 - Infusion adverse events CTCAE grade 3-5 (see clarifications)
- If Tysabri:
 - If a pause in treatment for longer than 8 weeks, register this as a period of no treatment and enter date for last dose + date for resumption of therapy

¹Aubagio, Avonex, Betaferon, Copaxone, Extavia, Gilenya, HSCT/BEAM, HSCT/CYK, Lemtrada, MabCampath, Mabthera, Mitoxantrone, Plegridy, Rebif, Study Drug, Tecfidera, or Tysabri

²Switch between injectable drugs (IFN, Copaxone)

Relapses

- **From: 24 months before start of inclusion therapy**
- Date
- Confirmed by
- (If available: Steroid therapy, Isolated ON, only afferent (not ON), monofocal relapse, complete remission within 12 months)

MRI (brain and spinal cord)

- **From: MRI brain closest in time before start of inclusion therapy**
- **From: MRI spinal cord closest in time before start of inclusion therapy**
- Date
- Number of T2 lesions (1, 2, 3, 4, 5, 6, 7, 8, 9, 10-20, or >20)
- Number of new T2 lesions + date of the reference MRI used
- Number of Gd+ lesions (exact number, leave blank if not contrast MRI)
- *Uncertain (possible) lesions not recorded*

EDSS (Register as in Figure 1 under Clarification)

- **From: 6 months before start of inclusion therapy**
- Date
- EDSS as specified in the clinical chart, alternatively
- EDSS calculated from clinical chart entries, see instructions

MSIS-29, EQ5D, SDMT, MS-kollen, FSMC, TSQ

- **From: 6 months before start of inclusion therapy**
- Date
- Values for each scale

Register the patient as a participant in the study

When the patient review is **complete**, select “**Retro_COMBAT-MS**” under studies (Note, NOT “Prosp_COMBAT-MS”) and enter the date when the clinical chart review was completed.

Clarifications

Patient lists

The patient lists are sent as encrypted Excel files. You unlock the file with the password you have received. The file contains a list of the patients belonging to your centre. All you need in the table is the column with the **personal identification number** [personnummer], so that you can find the patients in the clinical chart system and the MS register. The other columns can be ignored. Table 1 shows the table structure.

Patientlistornas struktur

tillhorighet	personnummer	patientkod	pal	inlusion_1st_DMT	inlusion_2nd_DMT
...
...
...
...

Inclusion

1. Has an inclusion therapy, i.e. the first disease modifying therapy³ initiated after 2011-01-01
2. A maximum of 1 disease modifying therapies before the inclusion therapy⁴
3. CIS/Relapsing-remitting MS at start of inclusion therapy, NOT primary or secondary progressive MS

Examples: Interferon introduced 2008, switch to Copaxone in 2009, and switch to Tysabri in 2011, meets the criteria with Tysabri as inclusion therapy (switch from Interferon to Copaxone counts as only 1 therapy). Tysabri introduced in 2008 and switch to Gilenya 2012, meets the criteria with Gilenya as inclusion therapy. Interferon introduced 2008 and switch to Tysabri in 2010 does not meet the criteria, because the patient has no therapy that *started* after 2011-01-01.

Disease debut and relapses

If the disease debut is within the study period, it is important not to forget to register the debut **relapse**, in addition to the actual disease debut. This is not automatically done by recording the debut date.

Inclusion therapy

In this project, inclusion therapy is the therapy that included the patient in the study according to the inclusion criteria, Item 1. Enter it into the register just like any other therapy.

³Aubagio, Avonex, Betaferon, Copaxone, Extavia, Gilenya, HSCT/BEAM, HSCT/CYK, Lemtrada, MabCampath, Mabthera, Mitoxantrone, Plegridy, Rebif, Study Drug, Tecfidera or Tysabri

⁴Switch between injectable drugs (IFN, Copaxone)

Disease modifying therapy

Disease modifying therapy (DMT), in this context, only includes:

- Aubagio
- Avonex
- Betaferon
- Copaxone
- Extavia
- Gilenya
- HSCT/BEAM
- HSCT/CYK
- Lemtrada
- MabCampath
- Mabthera
- Mitoxantrone
- Plegridy
- Rebif
- Study drugs
- Tecfidera
- Tysabri

Ivlg, pulsed cortisone, and placebo are not counted as therapy.

Date of start/end of therapy

Start date is the date of the first administration of the therapy. E.g. the date of the first infusion of Mabthera. Date for end of therapy is the date of the last administration of therapy. Administration of therapy is not recorded for all therapies and may have to be estimated to the date the patient has stopped taking the therapy.

Special instructions for certain therapies

- **Lemtrada:** Start date is registered as the date of first infusion in the first cycle. Each daily infusion is then recorded individually in the register for the first and second, and possibly third cycle. The end date is not registered and following therapies will thus run in parallel with Lemtrada
- **MabCampath:** See Lemtrada
- **HSCT:** Record date for stem cell infusion as start date. The end date is not registered and subsequent therapies will thus run parallel with HSCT
- **Mabthera:** Register the date and dose for each infusion. For longer pauses in infusions where the intention is to resume therapy, for example due to pregnancy or expectancy, therapy is not recorded as ended.
- **Study drug:** Can not be included if the study is still blinded. If, however, the drug given has been revealed, then this drug is registered as a therapy parallel with the study therapy already in the register.
- **Tysabri:** Each dose need not be specified, but register a pause in therapy if more than 8 weeks between infusions. To register a pause in therapy means ending the therapy on the date of the last infusion before the pause and to resume the therapy on the date of the first infusion after the pause.

No therapy

If there is an active decision to abstain from further therapy, then this is recorded as “No therapy” in the therapy module. However, this should not be done after Lemtrada/MabCampath and HSCT, because these therapies are not ended and therefore continue to apply.

CTCAE

The National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology that can be used in the reporting of adverse events (AE). One grading/severity scale exists for each AE term. To download the latest version of CTCAE (v. 4.03) and for more information, please see <https://evs.nci.nih.gov/ftp1/CTCAE/About.html>. Direct link to CTCAE in booklet format: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Infusion adverse events

Registered according to CTCAE (see above) with the AE term “Infusion related reaction”, under the category “General disorders and administration site conditions”. Only adverse events of CTCAE grade 3-5 need to be recorded. Reporting takes place in the comment field for the current therapy with the code “[YYMMDDCN]”, i.e. within brackets (without quotation): Year, Month, Day, followed by a C (for CTCAE) and one digit for the grade (3-5) according to CTCAE. If there is already text in comment field, this code is added to this text, preferably at the end.

Examples: *Anaphylactic reaction during the infusion has required adrenaline, 15 February 2017. Thus, a life-threatening consequence has demanded an emergency intervention; This is then classified as an “Infusion related reaction” of grade 4, according to CTCAE, and reported in the comment field as “[170215C4]” (without quotes).*

Registration of conversion to SPMS

Secondary progression (SP) is defined as a clinical condition with slow (continuous) progression during at least one year without distinct remission. Progression is detectable through comparison of clinical status between months or years, but not weeks or days. Repeated standardized walking tests, such as the 6-minute-walk test, that show continuous deterioration of at least 20% can also be taken as a sign of transition to SP phase. The transition to SP can usually be estimated with 1-2 years precision. A helpful criterion is that one common symptom in the progressive phase is a slowly developing central para/tetraparesis as part of a pyramidal syndrome including increased muscle tone with para/tetra propagation. The progressive debut can also be a progressive cerebellar syndrome or a progressive encephalopathy with increasing cognitive dysfunction. The estimated year for progress debut is recorded, not the year when a note about this is introduced in the clinical chart.

MRI

MRI brain and MRI spinal cord are recorded as separate entities. Registration begins with the MRI closest before the start of the inclusion therapy.

Example: *Start of inclusion therapy 160601. MRI brain before therapy 160101 and 160301. MRI spinal cord before therapy 150301 and 150901. Then MRI brain 160301 and MR spinal cord 150901 are recorded, as well as all MR brain and spinal cord examinations made after the start of the inclusion therapy (160601).*

If the MRI is done with contrast but no Gd+ lesions can be seen, register 0 Gd+ lesions. If the MRI is done without contrast, leave the number of Gd+ lesions blank. If the answer is uninterpretable (i.e. unclear about the number of new lesions), enter date, but leave the other fields empty.

Relapses

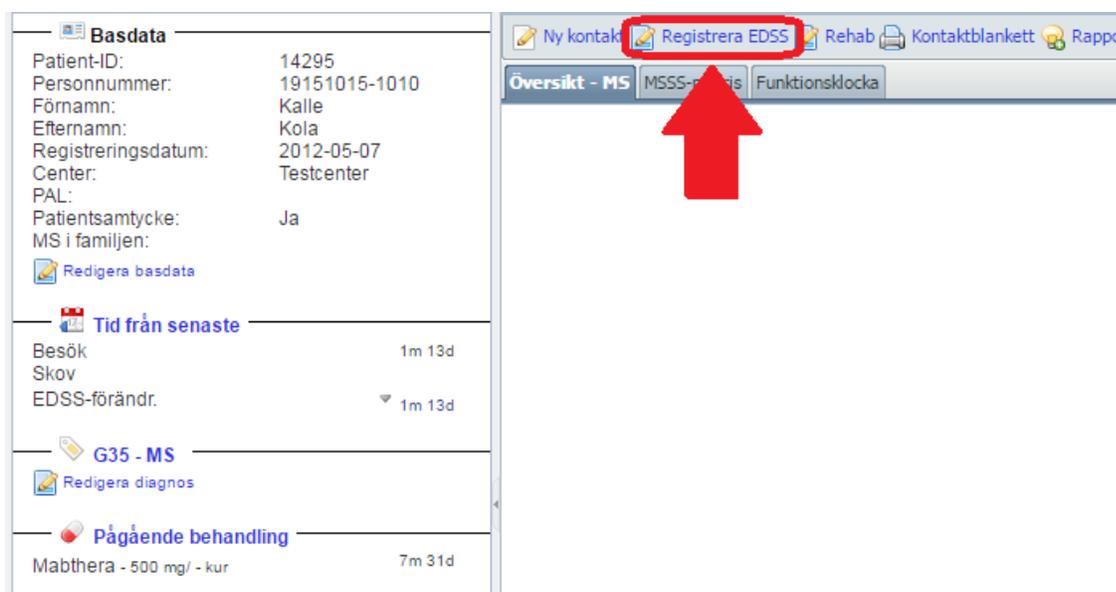
Defined as subacute new neurological symptoms consistent with MS, duration longer than 24h, and stable symptoms for the previous at least 30 days. The symptoms should not be better explained by a pseudo-relapse caused by fever, stress, etc. Worsened symptoms can be considered as a relapse if there are objectively clear impaired functions, and lack of factors associated with pseudo-relapse. New or progression of fatigue should not be counted as a relapse, unless it can be demonstrated by other simultaneous findings.

Estimation of EDSS

If EDSS is listed in the clinical chart this is recorded in the MS register. If EDSS is missing but there is a detailed neurological examination, EDSS can be estimated with regard to the functional domains: cranial nerves, pyramidal paths, sensory function, cerebellar function, urinary tract, mental function. If eye sight is missing, it can be assumed that FS for eye sight is O. If eye sight is specified, then count this with the converted score according to the EDSS template. We strive to get as uniform as possible assessments of EDSS across all centres and therefore recommend that each centre has an internal review of how to rate EDSS, with help of the [overview of functional scales at the SMSreg's website](#).

Registration of EDSS

EDSS should be registered under the EDSS section in the MS Register. Thus, not as part of a patient visit (where it has been registered previously). See Figure 1.



EDSS is registered under its own title

Questions and answers

- An instruction is unclear or there's something I don't understand. What do I do?
- Where should I register the data that I collect from the clinical chart?
- Do I need to check that the values already in the MS register match the values from the clinical chart?
- If a value in the MS register appears to be incorrectly filled in, can I change it?
- There is a value, eg EDSS, located just outside the interval we are supposed to examine which I would still like include. What do I do?
- How do I check that the patient had relapsing-remitting MS at the start of the inclusion therapy?
- Do I need to register infusions also for Tysabri?
- How do I find mabthera/tysabri infusions in the clinical charts?
- What adverse events should I register?
- The CTCAE rating is unclear, how can I differentiate grade 2 and grade 3?
- How should I estimate EDSS from the clinical chart?
- Where should I register EDSS?

An instruction is unclear or there's something I don't understand. What do I do?

Send an email to the contact person, Fredrik Piehl, at fredrik.piehl@ki.se and describe the problem. Then put the patient aside until we have been able to solve the issue.

Where should I register the data I collect from the clinical chart?

All data should be registered directly in the MS register. That means that we do not use any form of Excel document or other method of intermediate data storage.

Do I need to check that the values already in the MS register match the values from the clinical chart?

Only for therapy start/end date so that those match our definition (see clarifications below). For all other variables there is no need to check the values already in the MS register and no changes have to be made to data already in the MS register (except for therapy start/end).

If a value in the MS register appears to be incorrectly filled in, can I change it?

If a value (eg EDSS) is clearly incorrectly recorded in the MS register, compared to the clinical chart, this value can be corrected. If you are uncertain, however, it is better to leave the original value in the register.

There is a value, eg EDSS, located just outside the interval we are supposed to examine which I would still like include. What do I do?

It is OK to enter this value into the MS register, but it is then important to *not* change the date of the value to better fit our criteria. Register value and date just as specified in clinical chart.

How do I check that the patient had relapsing-remitting MS at the start of the inclusion therapy?

1. Check current disease progression: if RRMS -> OK
2. If SPMS, check the variable "to SPMS": If the year is later in time than start of inclusion therapy -> OK

Do I need to register infusions also for Tysabri?

No, infusions need only be registered for Mabthera and Lemtrada/MabCampath. However, the infusions for Tysabri should be checked and if there is a pause longer than 8 weeks, this should be registered as a pause in therapy. To register a pause in therapy means ending the therapy at the date of the last infusion before the pause and to restart the therapy at the date of the first the infusion after the pause.

How do I find mabthera/tysabri infusions in the clinical charts?

How this is recorded differs between the hospitals. In some cases this may be found in the nurse's charts.

What adverse events should I register?

The only adverse events to be recorded are infusion adverse events of CTCAE grade 3-5, associated with Mabthera infusions, as well as adverse events as a reason for end of therapy.

The CTCAE rating is unclear, how can I differentiate grade 2 and grade 3?

The difference between grade 2's and grade 3's first item (see below) is that, for grade 3, the symptoms and/or the infusion interruption should be "prolonged" ("Prolonged - not quickly responsive to symptomatic medication and/or brief interruption of infusion"). Here it can be discussed what is meant by "rapidly responsive" and "brief interruption". We define this as a response within 1 hour from the start of symptomatic treatment and/or regression of symptoms within 1 hour after infusion interruption, should be classified as grade 2. If the patient needs to stay for observation >3 hours in addition to clinical routine, then it is rated as grade 3.

CTCAE criteria:

Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated

Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic therapy (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <= 24 hrs

Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death

How should I estimate EDSS from the clinical chart?

See paragraph in the clarifications section, for instructions for estimating EDSS from clinical charts.

Where should I register EDSS?

EDSS should be registered under its own heading, **EDSS**, in the MS register. Thus, not as part of a patient visit (where it has been registered before). See Figure 1 under explanations.

Participating investigators and contributing researchers

Coordinating responsible researcher (contact person)

Fredrik Piehl, MD/Professor

Karolinska University Hospital, Solna, Stockholm

Deputy responsible researcher

Anders Svenningsson, doc/MD

Danderyd's hospital

Project Coordinator

Anna Fogdell-Hahn, doc

Karolinska Institutet, Stockholm

IMSE Coordinator, Mabthera

Suvi Virtanen, suvi.virtanen@ki.se

Data management team

Thomas Frisell, PhD

Peter Alping, MSc

Karolinska Institutet, Stockholm

Stockholm County

Katharina Fink, Associate Professor

Karolinska University Hospital Huddinge, Stockholm

Uppsala County

Joachim Burman, MD/Associate Professor

Uppsala Academic Hospital

Region Östergötland

Magnus Vrethem, MD/Professor

Linköping University Hospital

Region Skåne

Petra Nilsson, MD/Associate Professor

Skåne University Hospital, Lund

Region Västra Götaland

Jan Lycke, MD/Professor

Sahlgrenska University Hospital, Gothenburg

Västerbotten County

Jonathan Salzer, MD/Associate Professor

Norrland's University Hospital, Umeå

Region Örebro County

Martin Gunnarsson, MD/PhD

Örebro University Hospital