



**UNIVERSITY OF THESSALY**  
**School of Medicine**



**NET-MS**

**2011**

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An expert information system which has been developed to identify whether certain treatments in Multiple Sclerosis (MS) are associated with better outcome in terms of efficacy and safety

<http://netms.med.uth.gr>

LARISSA, 2011

## FAQs and Users' manual

### **(1) What is NET-MS?**

### **(2) How NET-MS is being used?**

### **(3) More**

### **(1) What is NET-MS?**

NET-MS is an expert information system which has been developed to identify whether certain treatments in Multiple Sclerosis (MS) are associated with better outcome in terms of efficacy and safety.

#### **1a. Why should a network system be useful?**

For a given clinical indication, clinicians and healthcare policy makers often have to choose between different active interventions (treatments). Many competing treatments have not been directly (head-to-head) compared in randomized controlled trials RCTs. Even when different interventions have been directly compared in RCTs such evidence is often limited and insufficient. This lack of evidence from direct comparison between the alternative treatments makes the decision of choosing a treatment difficult. Because of the lack of direct evidence, indirect comparisons have been recommended and used for evaluating the efficacy of alternative treatments.

#### **1b. What NET-MS provides to the clinicians?**

NET- MS provides the clinician the following:

- a) An updated catalogue with all published RCTs in MS for a specific treatment with information regarding the primary outcomes, safety, demographic and prognostic factors.
- b) Direct comparisons' data (data synthesis) for every possible treatment combinations available by synthesizing pre-existing published evidence.

- c) Indirect comparisons' data (including data synthesis) integrating data from direct and indirect comparisons which strengthens the power of evidence.

### **1c. Why is indirect analysis helpful?**

When there is no direct comparison, then the statistical methodology of multiple-treatments (network) meta-analysis may be applied to obtain some direct evidence of the relative efficacy of competing interventions, although the results of any indirect comparisons should be interpreted with great caution. The network meta-analysis methodology will allow: i) to synthesize the pre-existing published evidence, ii) to integrate data from direct and indirect comparisons and iii) to assess the strength and consistency of the evidence.

When the direct comparison is available, the indirect comparison is still useful: it provides more evidence. If there is no significant discrepancy in the results between the direct and indirect comparisons, the two results could be combined to obtain a more precise estimate. If there is significant discrepancy between the direct and indirect comparison, the validity of RCTs should be checked to investigate potential causes of discrepancy. A significant discrepancy between the direct and indirect comparison may be due to invalid result of the direct comparison, and /or the invalid results of the RCTs used in the indirect comparison.

### **1d. Which studies were excluded?**

- All non RCTs were excluded.
- All studies with results for treatment on acute relapse were also excluded.
- Cross-over studies which did not provide data for each period separately were also excluded. If cross-over studies did provide data from each study period separately, only data from first period were included in the analysis.
- Studies comparing different administration ways of the same drug or studies comparing different formulation of the same drug were excluded. Follow up period data and extension period data of RCTs were excluded.
- Post-hoc analysis and retrospective analysis data were not included.
- If an RCT was published in more than one article, the data provided in the final analysis were only included.

-If in a study, patients with different MS type were included and data for each MS type were provided, these were reported as separate studies.

### **1e. Which outcomes were reported?**

Binary outcomes were preferred.

Efficacy, which is clinicians' major concern, was tested in the 3 basic parameters:

1. Relapse
2. Disease progression
3. MRI lesions.

Safety results were also reported regarding

1. Adverse Events
2. Serious Adverse Events

#### *Efficacy outcomes*

1. Relapse: relapse free patients' data given in RCTs were used in NET-MS analyses.
2. Disease progression: Patients without disease progression were used in NET-MS analyses. EDSS score was the basic score preferred, with which patients were diagnosed to have progression.
3. MRI lesions: Patients without MRI lesions progression (all types of MRI lesions) were used in NET-MS. If an RCT provide data for MRI progression from more than one MRI lesions type, T2 lesions data were preferred.

#### *Safety outcomes*

1. Adverse Events: patients with Adverse Events data were reported.
2. Serious Adverse Events: patients with Serious Adverse Events were reported.

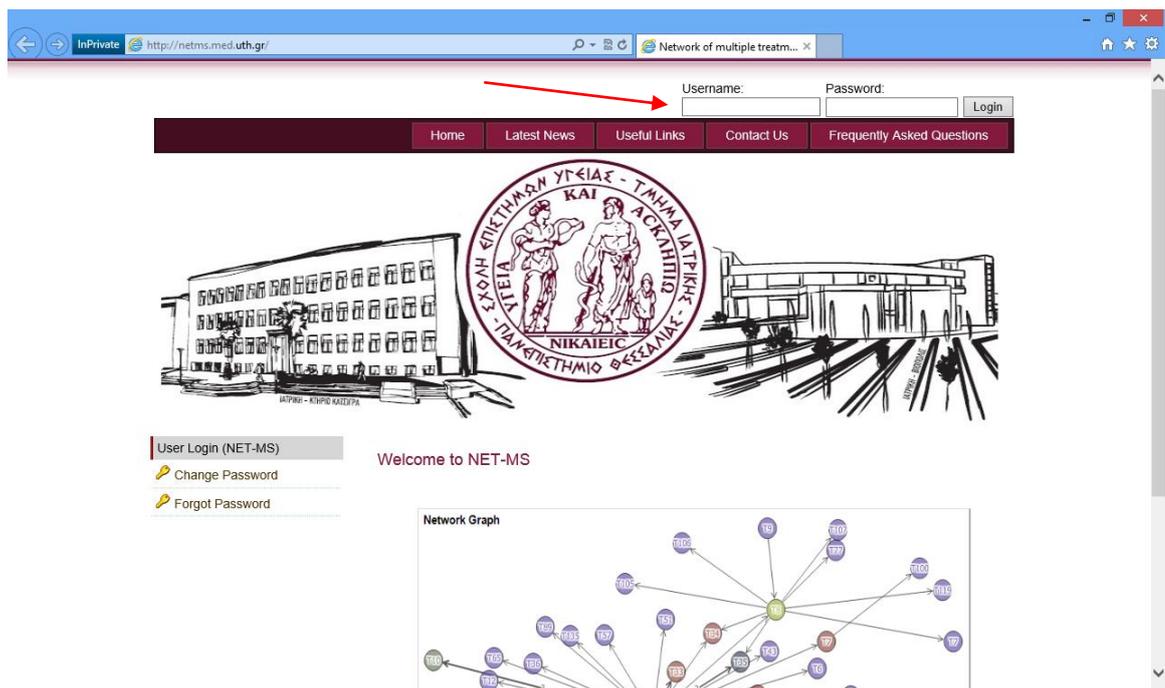
## (2) How NET-MS is being used?

A unique username and password is provided to the users. Only clinicians have access to the NET-MS. For this reason there is no option for account creation on the web site.

NET-MS is easy to use following next steps.

It is mandatory to go in a consecutive way through steps 1 >2>3>4.

### 1. Login to the site



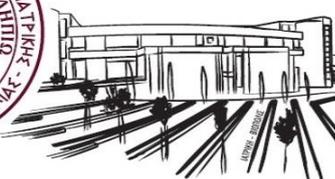
The screenshot shows the login page of the NET-MS website. The browser address bar displays <http://netms.med.uth.gr/>. The page features a navigation menu with links for Home, Latest News, Useful Links, Contact Us, and Frequently Asked Questions. A red arrow points to the login form, which includes fields for Username and Password, and a Login button. Below the navigation menu is a large circular logo with Greek text: "ΕΛΛΗΝΙΚΗ ΕΠΙΣΤΗΜΗ ΥΓΕΙΑΣ - ΤΑΧΥΜΑ ΙΑΤΡΙΚΗΣ - ΝΙΚΑΙΕΙΣ" and "ΕΛΛΗΝΙΚΟ ΚΑΙ ΤΑΧΥΜΑ ΙΑΤΡΙΚΗΣ - ΝΙΚΑΙΕΙΣ". The logo is flanked by two classical figures. Below the logo, there is a "Welcome to NET-MS" message and a "Network Graph" visualization. The Network Graph shows a central node connected to several other nodes, each labeled with a number (e.g., 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200). The Network Graph is a complex network of nodes and edges, with a central node (150) and many peripheral nodes. The nodes are labeled with numbers from 150 to 200. The edges represent connections between these nodes.

### 2. Choose an outcome (it is mandatory to be chosen before choose treatment of interest)

Browser address bar: <http://netms.med.uth.gr/default.aspx?id=27888EC7-EC41-4F05-BD04-06D1383DA667>

Logout

Home NET-MS Latest News Useful Links Contact Us Frequently Asked Questions



User Login (NET-MS)  
Change Password  
Forgot Password

Network of multiple treatments in Multiple Sclerosis  
**NET - M S**

Outcome: (Choose outcome)  
Patients with adverse events  
Patients without disease progression  
Patients without MRI progression  
Relapse free patients

Treatment of interest: [dropdown]  
Comparator treatment: [dropdown]

MS type: ALL [dropdown]  
Grouping MS: ALL [dropdown]  
Type of analysis: ALL [dropdown]



### 3. Choose a treatment of interest from the list provided

The screenshot shows the 'Network of multiple treatments in Multiple Sclerosis' (NET-MS) interface. On the left, there are navigation links: 'User Login (NET-MS)', 'Change Password', and 'Forgot Password'. The main area displays a list of treatments under various categories. A red arrow points to the 'Fingolimod 5mg' entry, which is highlighted in blue. Below the list, there are two buttons: 'Direct pooled analysis' and 'Indirect analysis'.

**Network of multiple treatments in Multiple Sclerosis**  
**NET - MS**

Outcome

Treatment of interest: **Fingolimod 5mg**

Comparator treatment

MS type

Grouping MS

Type of analysis

From year: ALL

SPC of treatment of

Published RCTs for treat

Type of analysis

Direct pooled analysis

Indirect analysis

### 4. Choose a comparator treatment from the list provided

The screenshot shows the same 'Network of multiple treatments in Multiple Sclerosis' (NET-MS) interface. The 'Fingolimod 5mg' entry is still highlighted in blue. A red arrow points to the 'Glatiramer Acetate 20mg (Copaxone)' entry, which is the first comparator treatment listed below the treatment of interest. Below the list, there are two buttons: 'Direct pooled analysis' and 'Indirect analysis'.

**Network of multiple treatments in Multiple Sclerosis**  
**NET - MS**

Outcome

Treatment of interest: **Fingolimod 5mg**

Comparator treatment: **Glatiramer Acetate 20mg (Copaxone)**

MS type

Grouping MS

Type of analysis

From year: ALL

SPC of treatment of

Published RCTs for treat

Type of analysis

Direct pooled analysis

Indirect analysis

### 5. Choose a MS type (optional)

**Network of multiple treatments in Multiple Sclerosis  
NET - MS**

User Login (NET-MS)  
Change Password  
Forgot Password

Outcome: Relapse free patients

Treatment of interest: Fingolimod 5mg

Comparator treatment: ALL

**MS type**

- ALL
- CPMS
- MIXED
- PPMS
- PPMS and SPMS
- PRMS and SPMS
- RRMS
- RRMS and CIS
- RRMS and PPMS and SPMS
- RRMS and PRMS
- RRMS and PRMS and SPMS
- RRMS and SPMS
- SPMS

From year: ALL

SPC of treatment of interest

SPC of comparator treatment

Published RCTs for treatment of interest

Type of analysis

- Individual RCTs direct analysis
- Direct pooled analysis
- Indirect analysis

### 6. Choose a year of interest (optional)

**Network of multiple treatments in Multiple Sclerosis  
NET - MS**

User Login (NET-MS)  
Change Password  
Forgot Password

Outcome: Relapse free patients

Treatment of interest: Fingolimod 5mg

Comparator treatment: ALL

**MS type**: ALL

Grouping MS: ALL

Type of analysis: ALL

From year: 1987

to year: ALL

SPC of treatment of interest

SPC of comparator treatment

Published RCTs for treatment of interest

Type of analysis

- Individual RCTs direct analysis
- Direct pooled analysis
- Indirect analysis

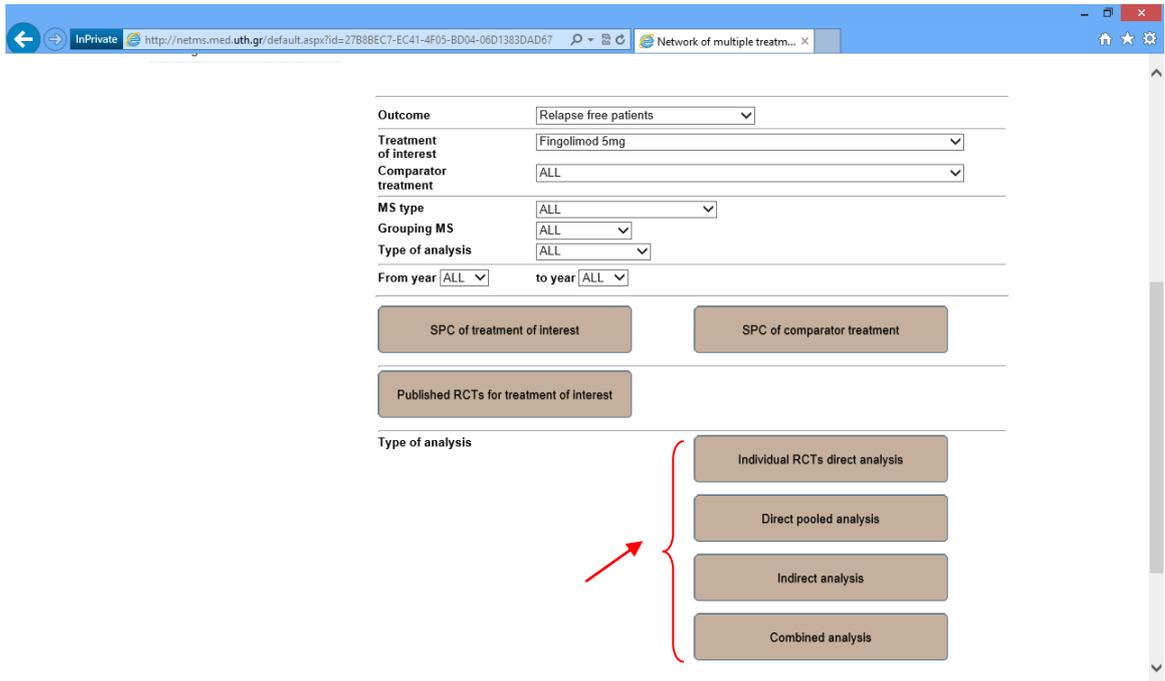
7. SPCs for treatment of interest and comparator treatment are available (optional). For details go on page 10

The screenshot shows the 'Network of multiple treatments in Multiple Sclerosis' (NET-MS) web application. The interface includes a navigation menu with 'User Login (NET-MS)', 'Change Password', and 'Forgot Password'. The main search area contains several dropdown menus: 'Outcome' (Relapse free patients), 'Treatment of interest' (Fingolimod 5mg), 'Comparator treatment' (ALL), 'MS type' (ALL), 'Grouping MS' (ALL), and 'Type of analysis' (ALL). Below these are 'From year' and 'to year' dropdowns, both set to 'ALL'. Two red arrows point to the 'SPC of treatment of interest' and 'SPC of comparator treatment' buttons. A 'Published RCTs for treatment of interest' button is also visible. The 'Type of analysis' section includes buttons for 'Individual RCTs direct analysis', 'Direct pooled analysis', and 'Indirect analysis'.

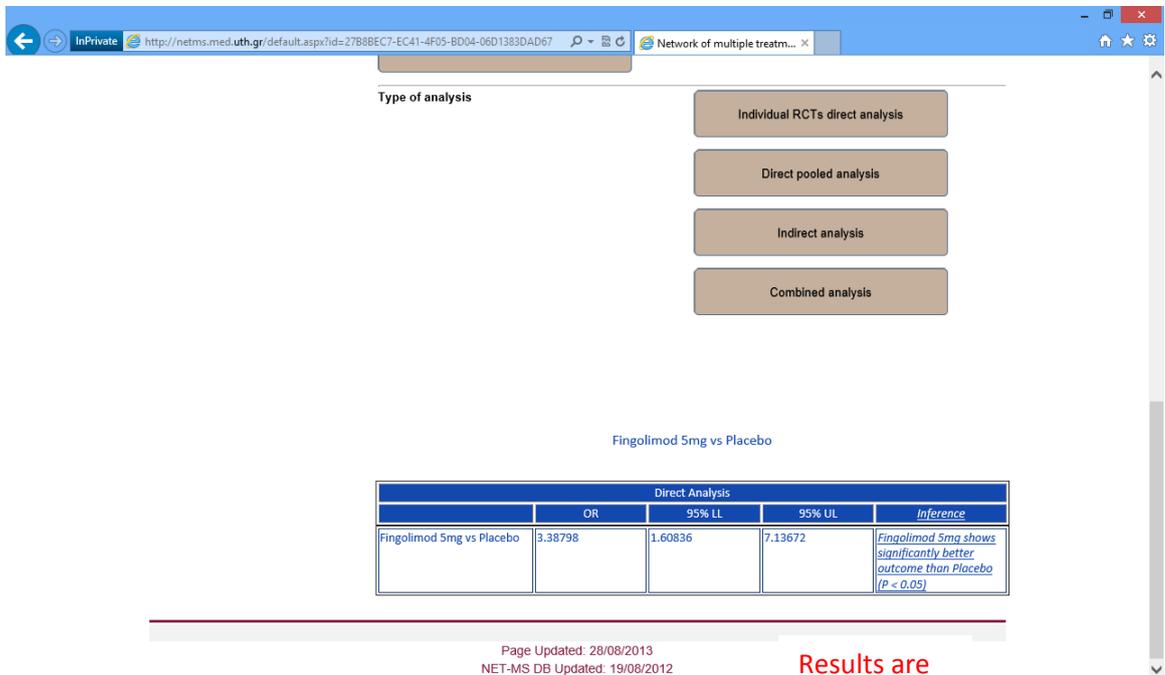
8. Published RCTs for treatment of interest are available (optional). For details go on page 12

This screenshot is similar to the previous one, showing the NET-MS web application interface. The search filters are the same. In this view, a red arrow points to the 'Published RCTs for treatment of interest' button. The 'SPC of treatment of interest' and 'SPC of comparator treatment' buttons are also present but not highlighted. The 'Type of analysis' section remains the same.

**9. Choose a type of analysis. (Please click only once on the button of your choice)**



**10. Wait until data appears to the screen. Please click only once (on your first choice and wait for the results). Then you may continue with your second, third and fourth choice)**



Results are presented as above

### **(3) More**

#### **3a. Type of analysis options**

##### *Individual RCTs direct analysis*

All RCTs that have been published comparing direct the selected treatments are displayed to year of publication.

##### *Direct pooled analysis*

All RCTs having been published comparing direct the selected treatments are used and meta-analysis results are provided. A direct meta-analysis is conducted and the random effects (RE) OR is calculated, according to DerSimonian and Laird. The RE model is used instead of the fixed effects model because it is more conservative. Heterogeneity between studies is tested using the Q-statistic, and it is quantified with the I<sup>2</sup> metric, which is independent of the number of studies included in the meta-analysis. Number of studies used is also provided.

##### *Indirect analysis*

In the indirect comparison of treatments selected (A and B), in which each treatment has been compared directly with a common treatment (C), the OR of A versus B was calculated as follows:  $\ln(\text{OR}_{A\text{vs}B}) - \ln(\text{OR}_{A\text{vs}C}) - \ln(\text{OR}_{B\text{vs}C})$ , and the respective 95% (CI) is estimated assuming asymptotic normality and lack of covariance, as described by Glenny et al and Song et al.

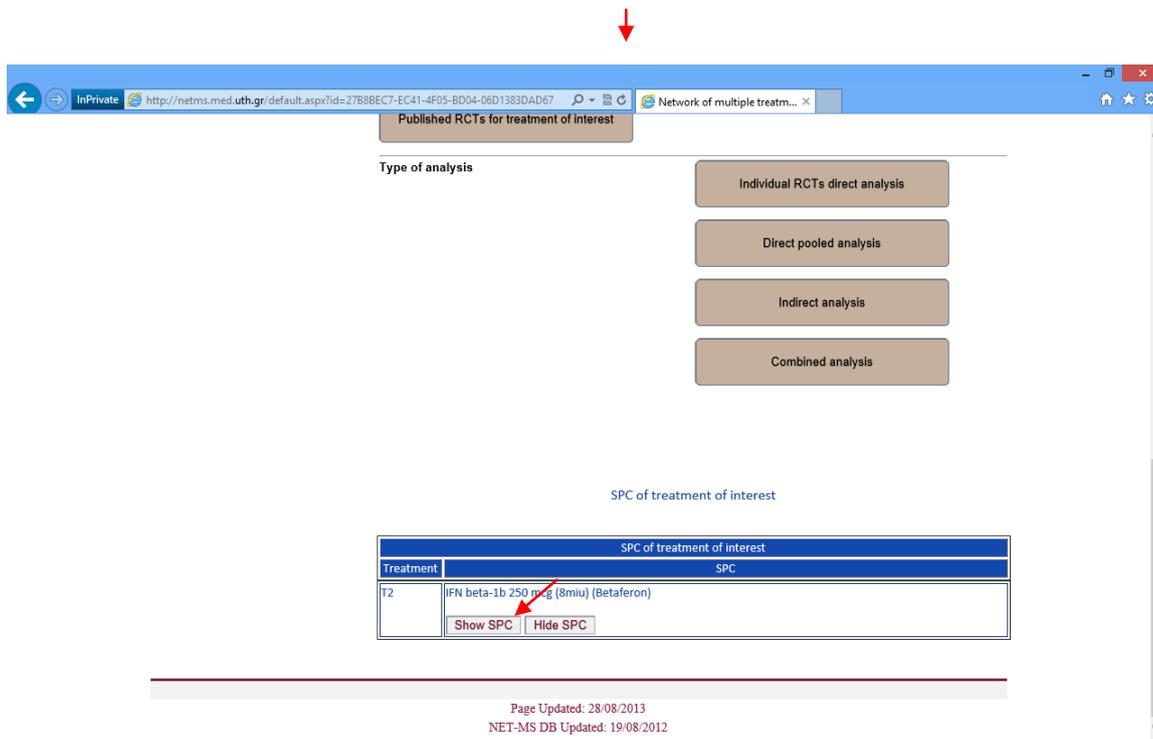
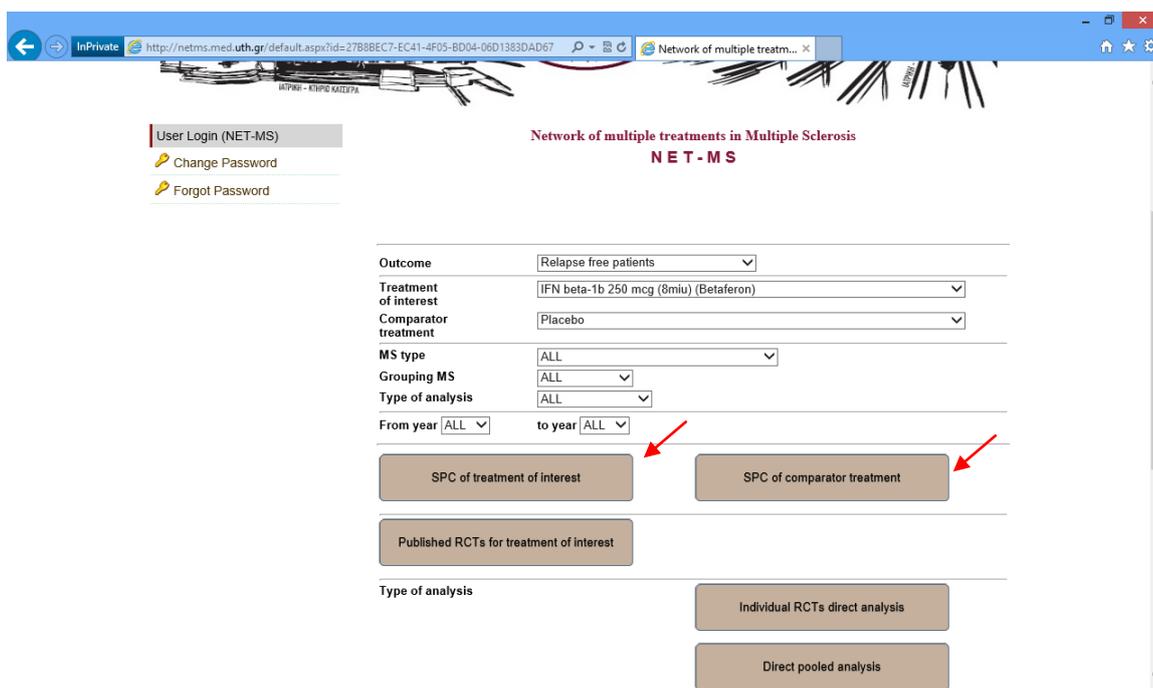
##### *Combined analysis*

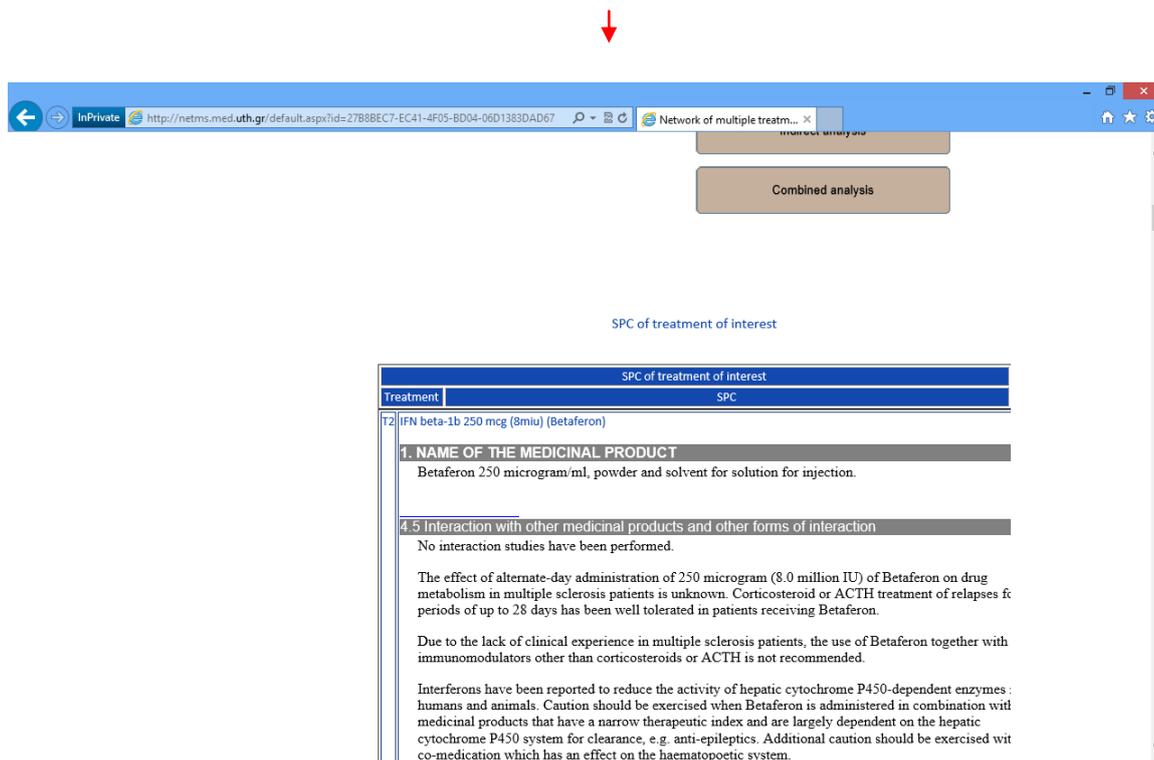
In combining the studies for direct or indirect comparisons, the inverse variance method was used, as described previously.

### 3b. What else can be found?

#### 3b-1. SPC of treatment of interest and comparator treatment

The user can retrieve the SPC of the selected treatments. SPC data are retrieved from the following web address: medicines.org.uk.

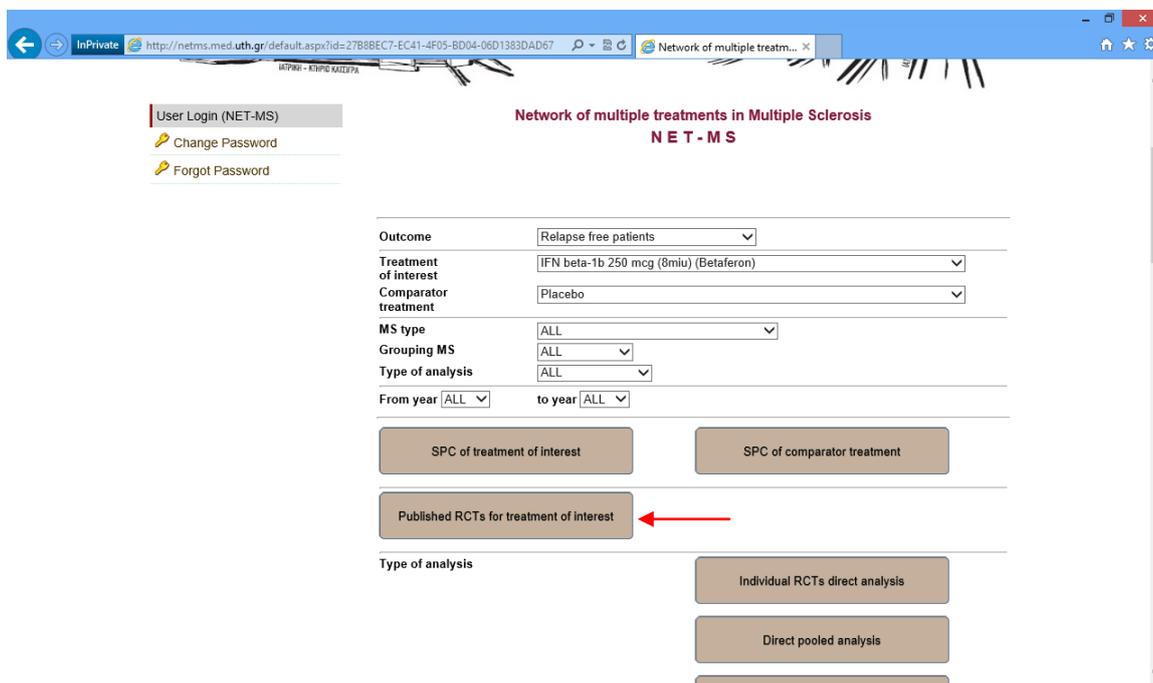




The electronic Medicines Compendium (eMC) contains up to date, easily accessible information about medicines licensed for use in the UK. The eMC has more than 7,000 documents, all of which have been checked and approved by either the UK or European government agencies which license medicines. These agencies are the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). All the information on the eMC website comes directly from pharmaceutical companies. eMC is being updated in 30 days' time after a new drug is launched or a change has been approved. Our site updates SPC data every 3 months.

### 3b-2. Published RCTs of treatment of interest

By clicking on “Published RCTs for treatment of interest” all published RCTs for the selected treatment of interest are appearing on the screen according to the year of publication.



Period	
From Year	To Year
1900	9999

Published RCTs

Published RCTs	
Author: Cadavid Year: 2009 Journal: Neurology Study name: BECOME MStype: RRMS and CIS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	Efficacy of treatment of MS with IFN -1b or glatiramer acetate by monthly brain MRI in the BECOME study Show full RCT Hide RCT
Author: O'Connor Year: 2009 Journal: LancetNeurol Study name: BEYOND MStype: RRMS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study Show full RCT Hide RCT
Author: Durelli Year: 2008 Journal: Jneurol Study name: OPTIMS MStype: RRMS Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)	The OPTimization of Interferon for MS Study: 375 µg interferon beta-1b in suboptimal responders Show full RCT Hide RCT
Author: Etamadifar	Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting



The abstract of each RCT appearing on the screen can be easily retrieved by clicking “Show full RCT”.

Combined analysis

Period	
From Year	To Year
1900	9999

Published RCTs

Published RCTs	
<p>Author: Cadavid                      Year: 2009                      Journal: Neurology                      Study name: BECOME                      MStype: RRMS and CIS                      Regimen: IFN beta-1b 250 mcg (8miu) (Betaferon)</p>	<p><b>Efficacy of treatment of MS with IFN -1b or glatiramer acetate by monthly brain MRI in the BECOME study</b></p> <p>Background: There are no published MRI studies comparing interferon beta 1b (IFN -1b) and glatiramer acetate (GA) for treatment of relapsing multiple sclerosis (MS). Objective: To compare the efficacy of IFN -1b and GA for suppression of MS disease activity as evidenced on frequent brain MRI. Methods: A total of 75 patients with relapsing-remitting MS or clinically isolated syndromes were randomized to standard doses of IFN -1b or GA and followed by monthly brain MRI for up to 2 years with a protocol optimized to detect enhancement. The primary outcome was the number of combined active lesions (CAL) per patient per scan during the first year, which included all enhancing lesions and nonenhancing new T2/fluid-attenuated inversion recovery (FLAIR) lesions. Secondary outcomes were the number of new lesions and clinical exacerbations over 2 years. Results: Baseline characteristics were similar between the groups. The primary outcome showed similar median (75th percentile) CAL per patient per scan for months 1–12, 0.63 (2.76) for IFN -1b, and 0.58 (2.45) for GA (p 0.58). There were no differences in new lesion or clinical relapses for 2 years. Only 4.4% of CAL on monthly MRI scans were nonenhancing new T2/FLAIR lesions. Conclusion: Patients with relapsing multiple sclerosis randomized to interferon beta 1b or glatiramer acetate showed similar MRI and clinical activity</p> <p>Show full RCT   Hide RCT</p>

### 3c. Which metrics are used and what do they mean?

The results of comparisons are presented as OR (odds Ratio) and 95 % CI (confidence interval). If  $OR > 1$  then the treatment of interest shows significantly better outcome; however, if the  $OR < 1$  then the treatment of interest shows significantly worse outcome than the comparator treatment. If the 95% CI of the OR contains the value of 1, then, the treatment of interest does not show significantly better or worse outcome than the treatment of interest. However, if the 95% CI of the OR does not contain the value of 1, then, the OR is significant, and the treatment of interest does show significant outcome as many times as the OR value.

Let choose as outcome the “Patients without disease progression”, treatment of interest the “Glatiramer Acetate 20 mg (Copaxone)” and comparator treatment the “Placebo”. Also, let select the “Indirect analysis” option. The results of the analysis are  $OR = 2.98668$  and 95% CI (1.76104- 5.06535). This finding imply that Copaxone is significantly 3-fold (3 times) better response (outcome) than placebo ( $OR = 2.99$ ) and this outcome is significant since the 95%CI does not contain the value of 1. An OR of 2.99, indicates in patients receiving Copaxone, there is more chance (3 times) of being without disease progression, than in patients receiving placebo.

In the field “**inference**” at the interface, the inference of the analysis along with the results are also shown, i.e. the OR and the respective 95%. CI.

#### Glatiramer Acetate 20mg (Copaxone) vs Placebo

Indirect analysis				
	OR	95% LL	95% UL	Inference
Glatiramer Acetate 20mg (Copaxone) vs Placebo	2.98668	1.76104	5.06535	Glatiramer Acetate 20mg (Copaxone) shows significantly better outcome than Placebo ( $P < 0.05$ )
Number of studies: 21				