UNIVERSITY OF THESSALY

School of Medicine

NET-MS 2011

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.

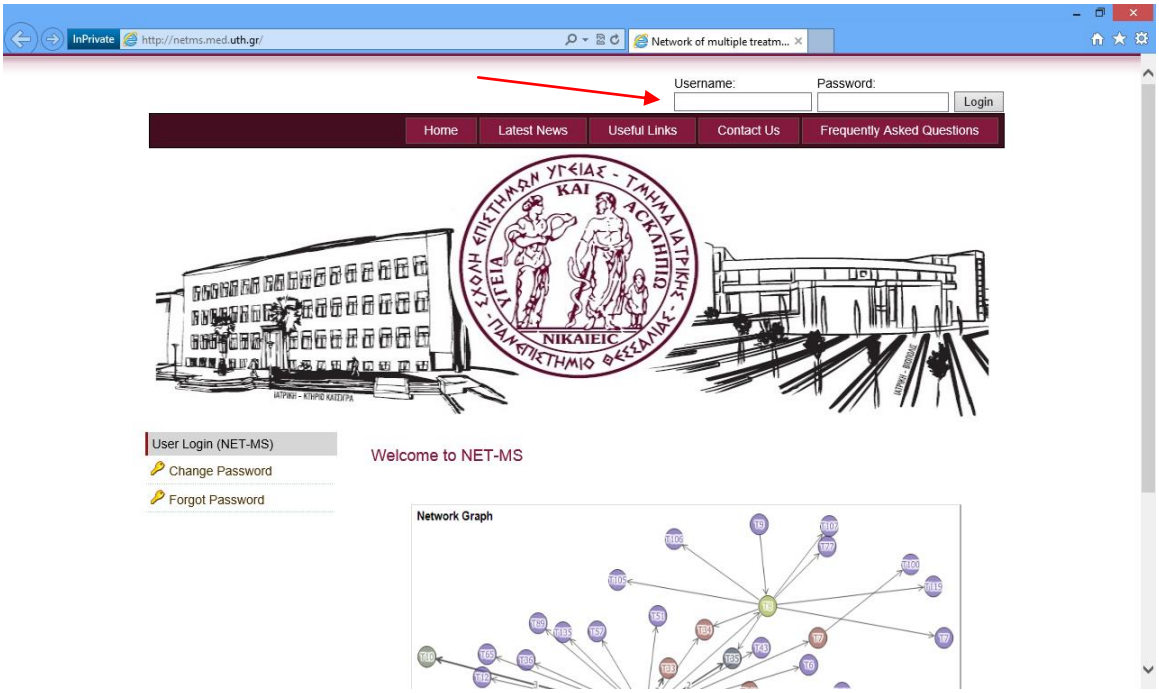
(2) How NET-MS is being used?

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.

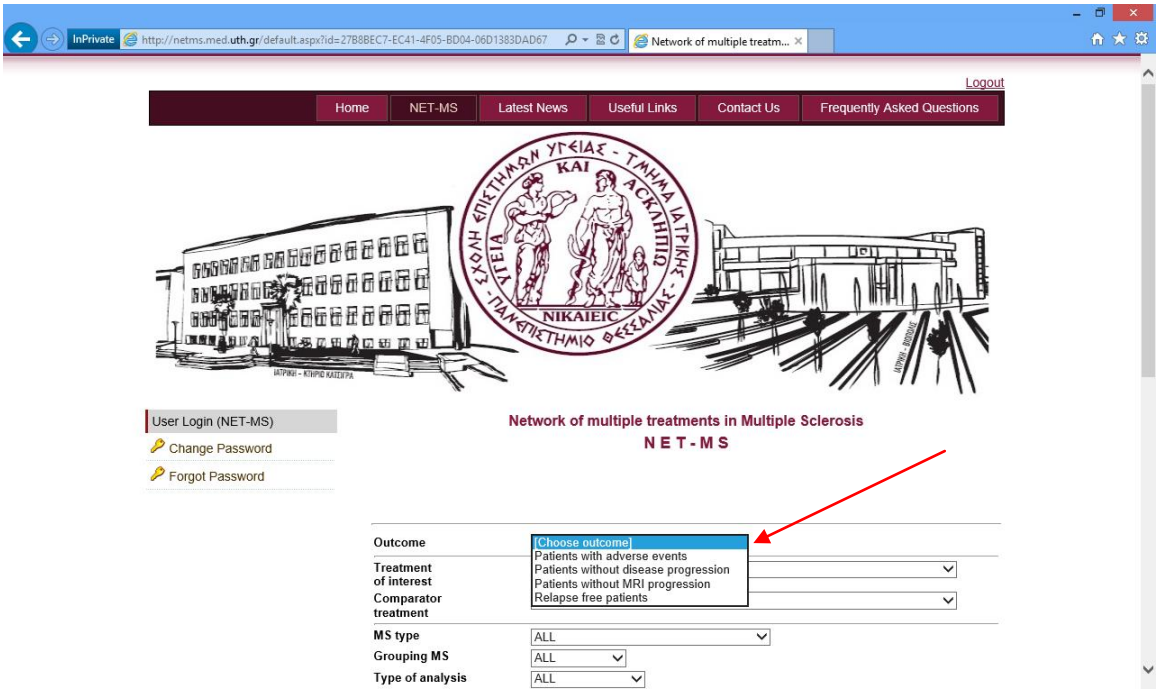
NET-MS is easy to use following next steps.

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

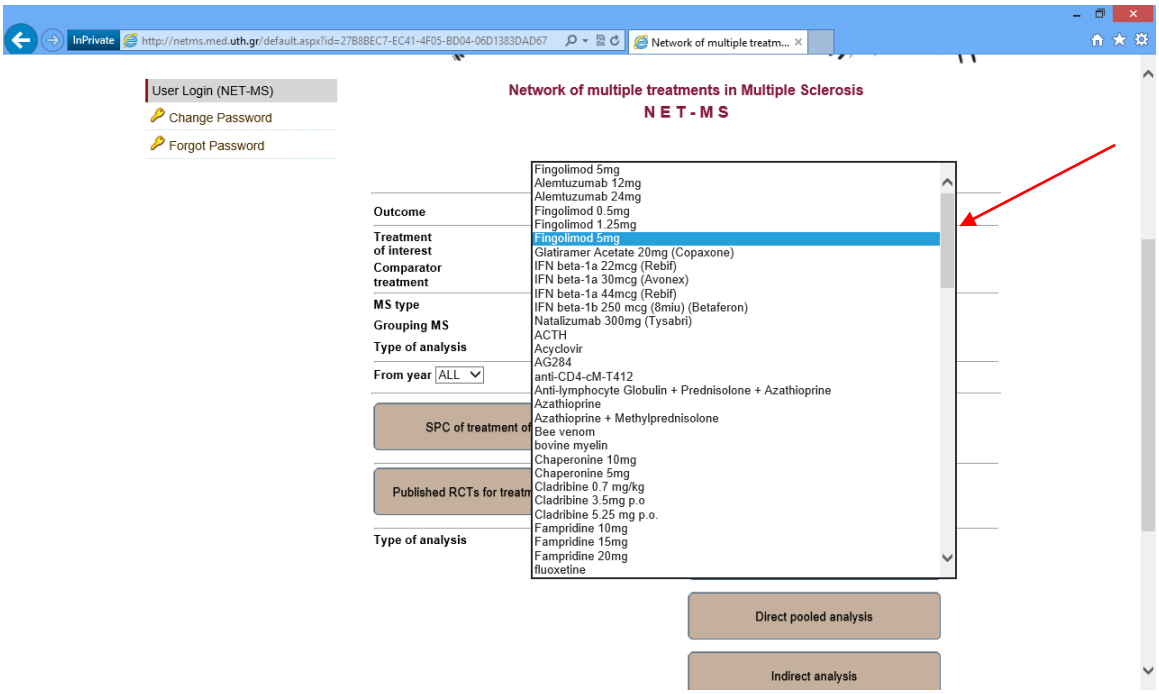
1. **Login to the site**



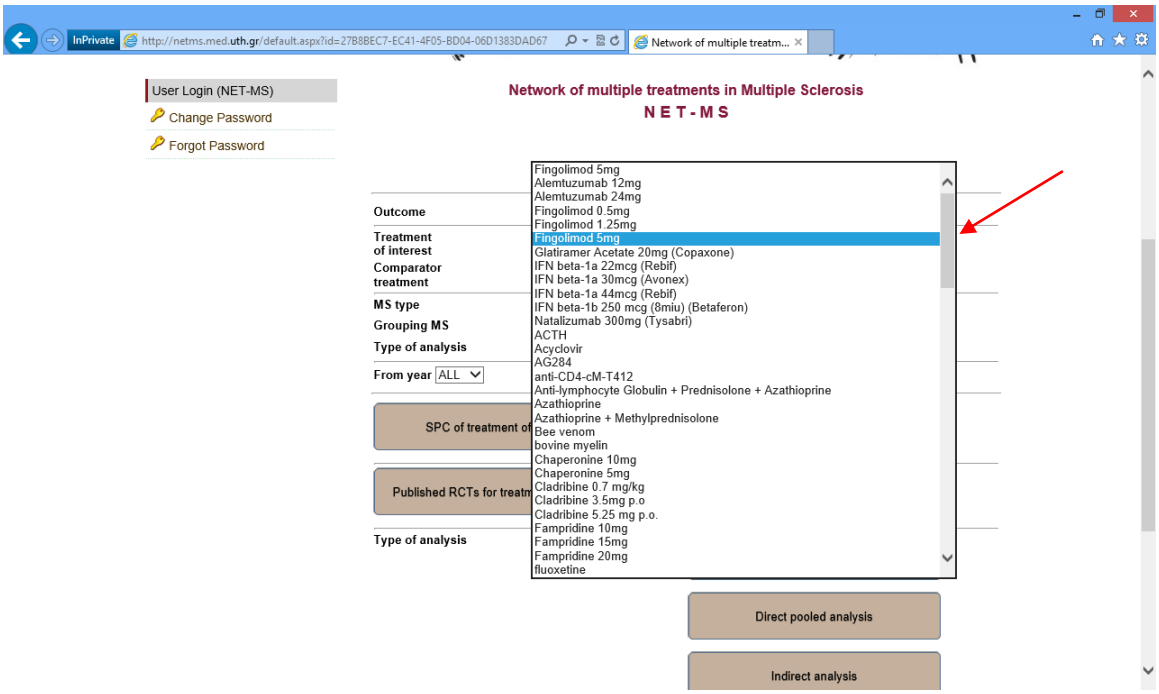
2. **Choose an outcome** (it is mandatory to be chosen before choose treatment of interest)


InPrivate
http://netms.med.uth.gr/default.aspx?id=27B8BEC7-EC41-4F05-BD04-06D1383DAD67
Network of multiple treatm...
Logout
Home
NET-MS
Latest News
Useful Links
Contact Us
Frequently Asked Questions
ΝΙΚΑΙΕΙΣ
User Login (NET-MS)
Change Password
Forgot Password
Network of multiple treatments in Multiple Sclerosis
N E T - M S
Outcome
[Choose outcome]
Patients with adverse events
Patients without disease progression
Patients without MRI progression
Relapse free patients
Treatment of interest
Comparator treatment
MS type
ALL
Grouping MS
ALL
Type of analysis
ALL

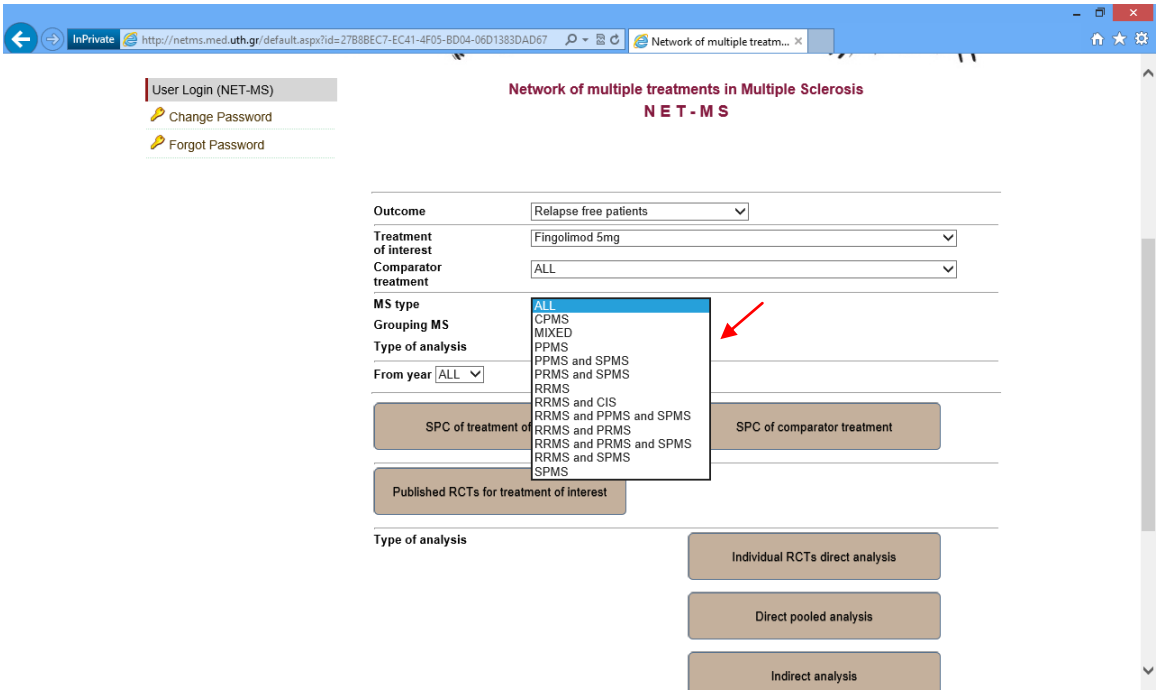
3. Choose a treatment of interest from the list provided



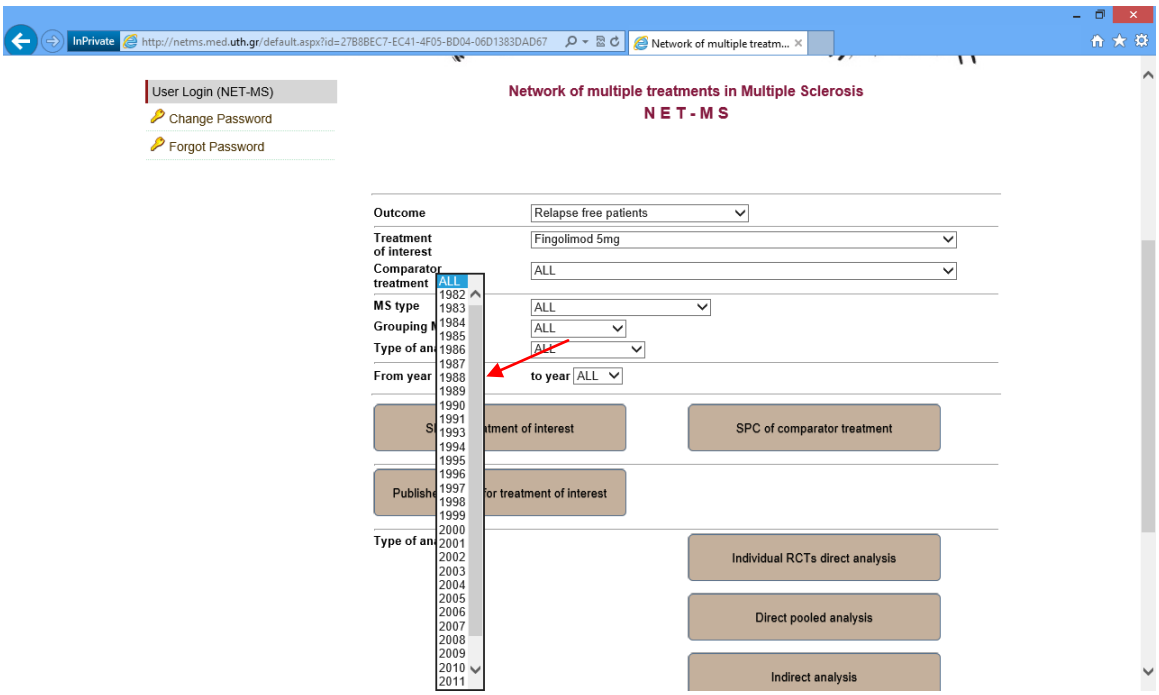
4. Choose a comparator treatment from the list provided



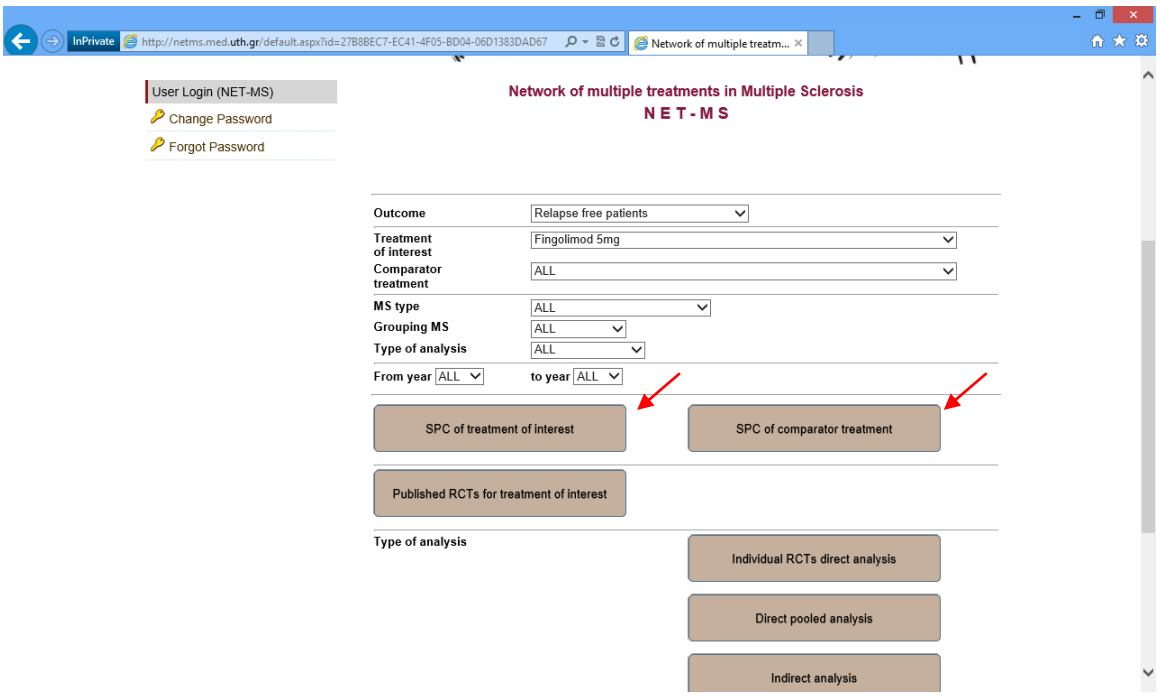
5. **Choose a MS type** (optional)



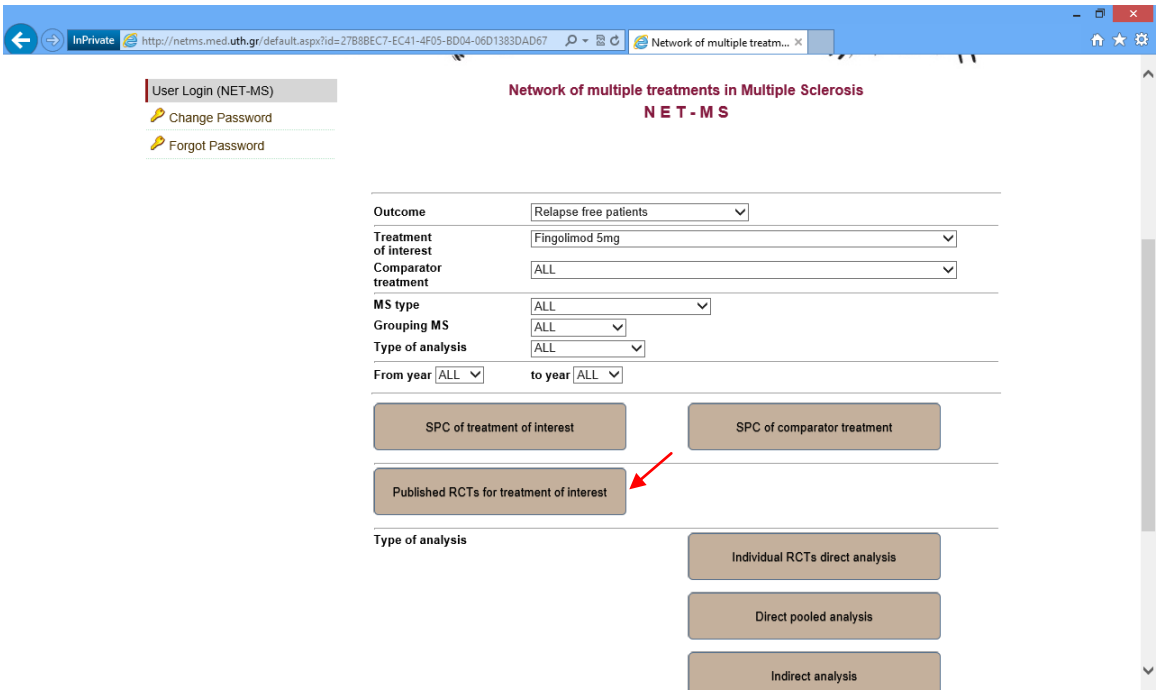
6. **Choose a year of interest** (optional)



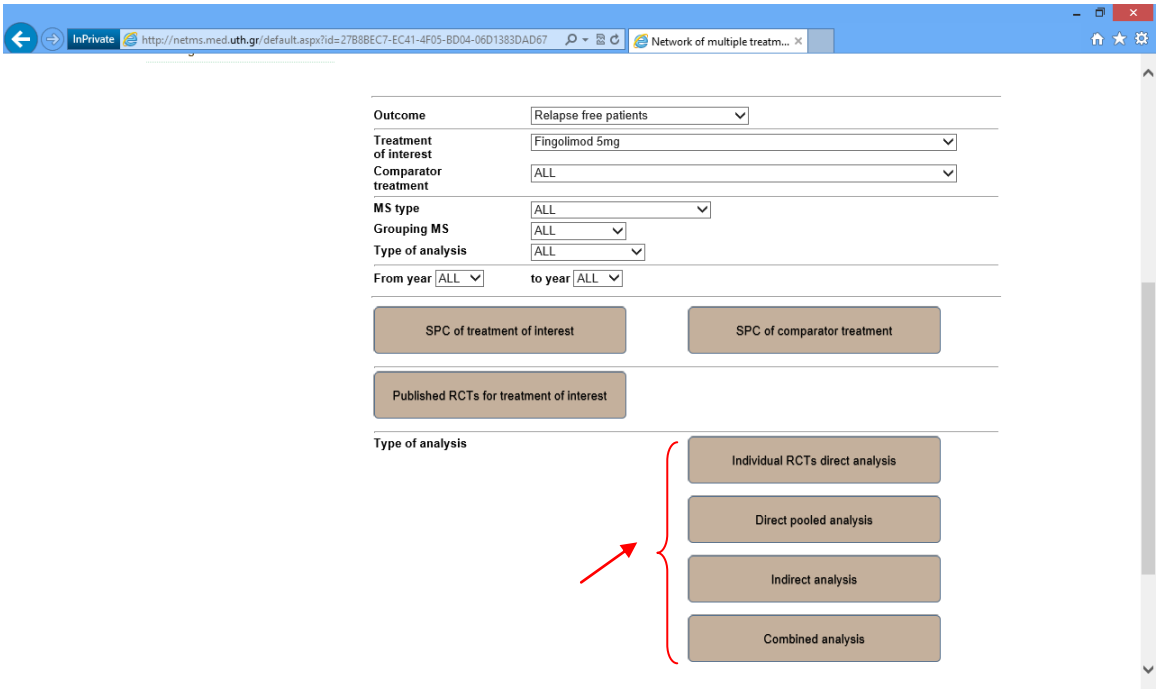
7. **SPCs for treatment of interest and comparator treatment are available** (optional). For details go on page 10



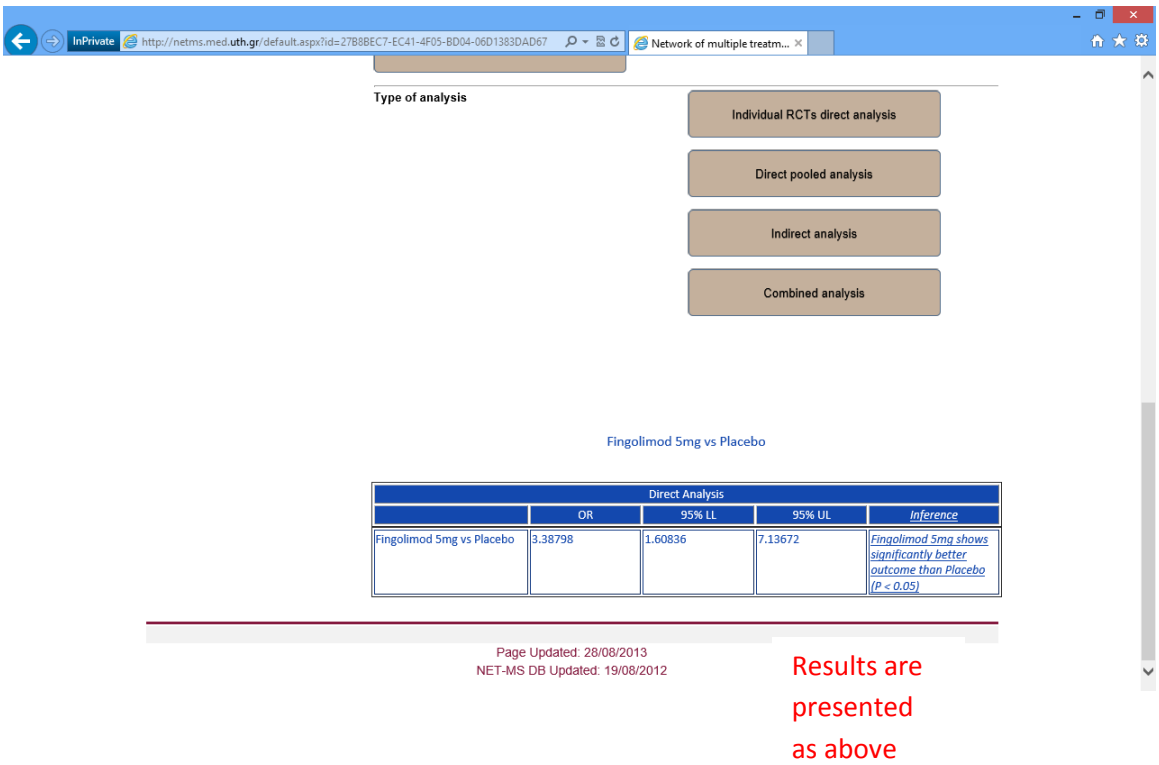
8. **Published RCTs for treatment of interest are available** (optional). For details go on page 12



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 I2 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(ORAvsB) _ ln(ORAvsC) – ln(ORBvsC), and the respective 95% (CI) is estimated assuming asymptotic normality and lack of covariance, as described by Glenny et al and Song et al.

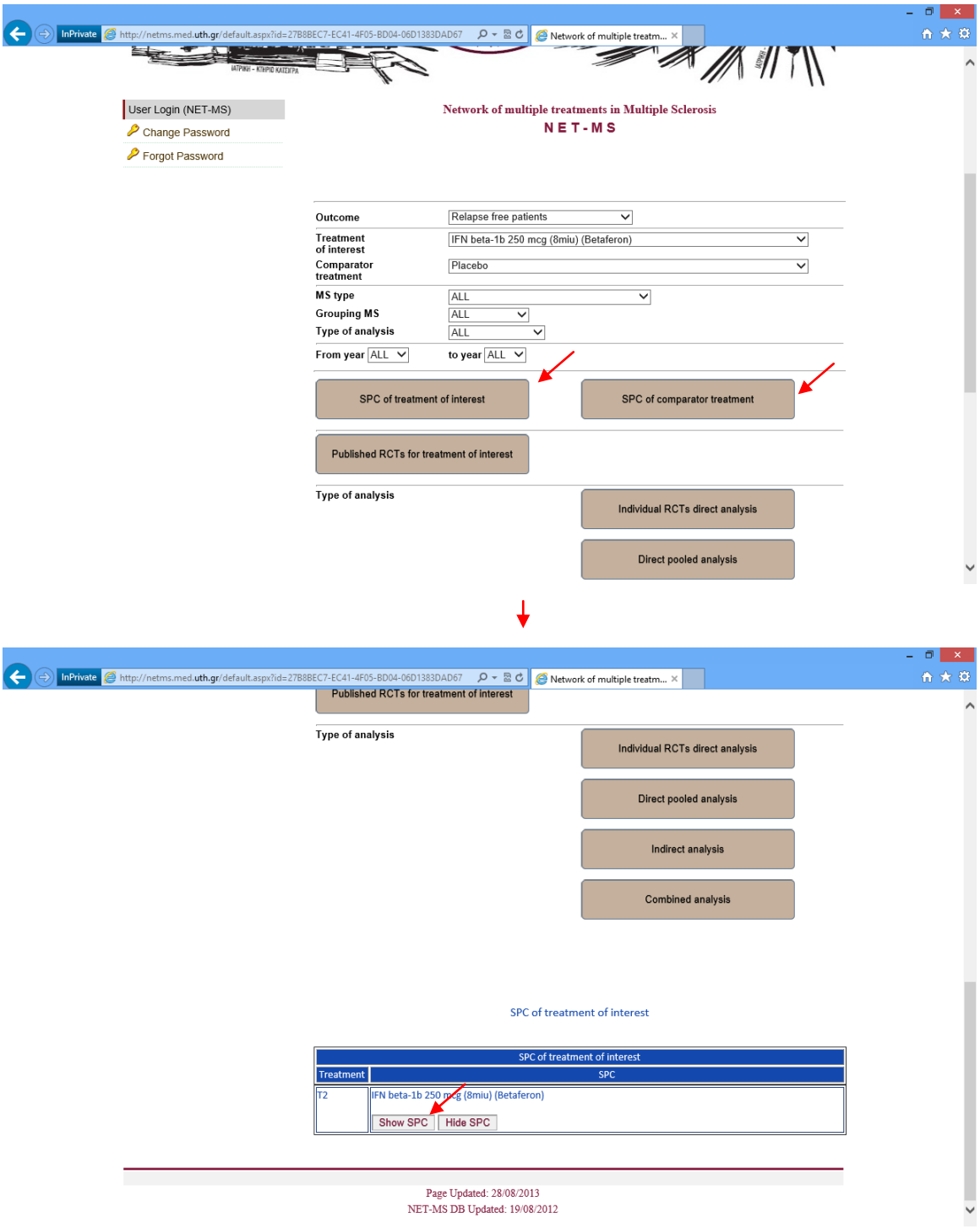
Combined analysis

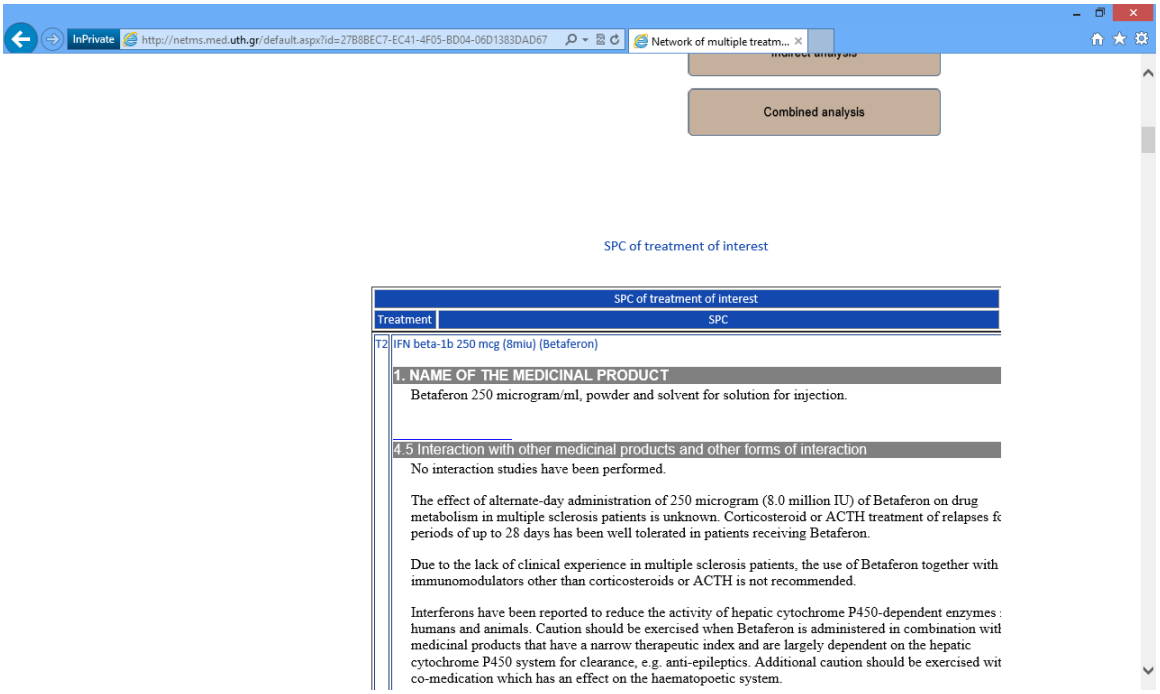
In combining the studies for direct or indirect comparisons, the inverse variance method was used, as described previously.

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.

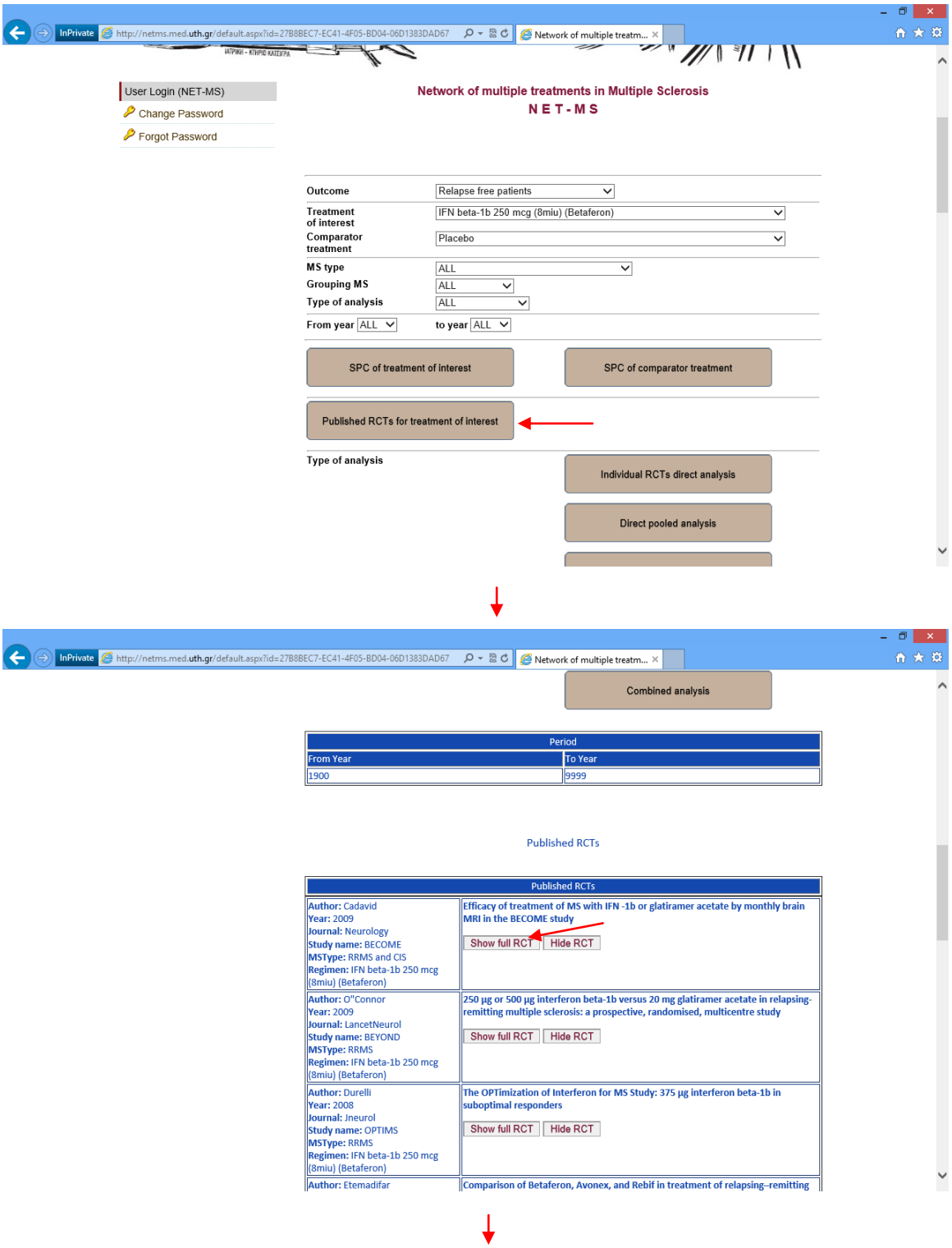




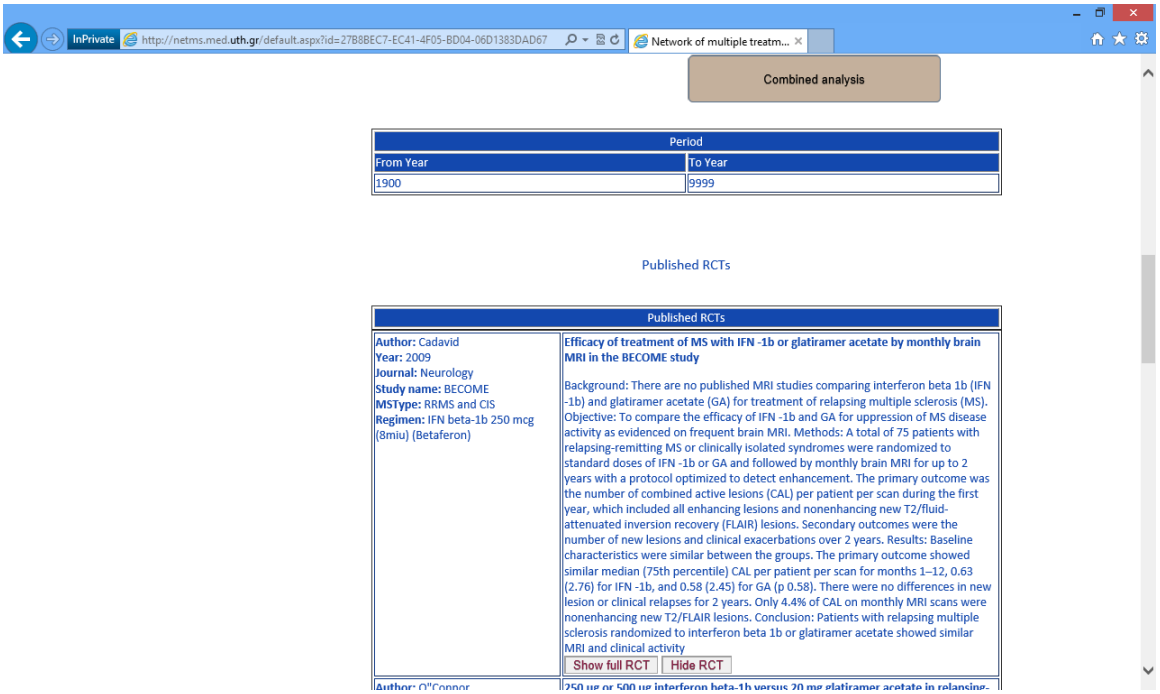
The electronic Medicines Compendium (eMC) contains up to date, easily accessible information about medicines licensed for use in the UK. The eMC has more than 7,000 documents, all of which have been checked and approved by either the UK or European government agencies which license medicines. These agencies are the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMEA). 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 changed 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.



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



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				