# SOLUTION: Network Meta-Analysis worksheet

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This practical uses the newly developed CRSU app *MetaInsight* which can be accessed from
https://crsu.shinyapps.io/metainsightc/

*MetaInsight* is a web-based App for conducting network meta-analysis for binary and continuous outcomes using fixed or random effects models. It may also be used to facilitate sensitivity analysis via the inclusion and exclusion of studies as this practical will demonstrate.

After completing this practical, you will be able to….

- Enter data into *MetaInsight*
- Perform a network meta-analysis in *MetaInsight* and interpret the results
- Examine the influence on the results when studies are included and excluded in a sensitivity analysis

In this practical you will be using a real network meta-analysis dataset comparing drug treatments and placebo for reducing obesity (*Gray LJ, et al. A systematic review and mixed treatment comparison of pharmacological interventions for the treatment of obesity. Obes Rev. 2012 Jun;13(6):483-98.*). Interest lies in which of the interventions is most effective for reducing weight. The outcome measure in each study arm is weight loss from study baseline in kilograms. (The whole dataset comes ready loaded into the App but you are going to start by only looking at a subset of the data and learning to load the data into the App).

Firstly, open the *MetaInsight* App in a web browser on your computer:

https://crsu.shinyapps.io/metainsightc/

The outcome for the analysis is continuous so click on "Continuous Data" at the top of the page. Here you will see a description of the format of the data required and two boxes in which data is entered (these will have data in already as the App comes with an example dataset already included for illustration purposes). The first box contains the main data. Each row contains information on a separate study. Columns indicate study ID, study name, then 4 variables each for up to 6 treatment arms indicating a treatment code, a sample size, a mean outcome (change in weight from baseline in our example) and corresponding standard deviation for each treatment arm. Treatments must be entered in descending number order with the reference treatment labelled as treatment 1. The second box includes the labels for each of the treatment codes.

The data for practical, presented in the correct format, is available in an Excel spreadsheet from:
http://www.nihrcrsu.org/courses%20and%20conferences/crsu__cochrane_workshop_2018/

## PART ONE:

Initially we are going to keep things simple by including only comparisons between three treatments: Orlistat, Sibutramine and Placebo.

i) Load the data from the Excel 'dataset' spreadsheet labelled '3-treatment data (Orlistat, Sibutramine, Placebo)' by copying and pasting it into the first box on *MetaInsight*. Note that you will need to enter the whole dataset allowing for 6 treatments with 'NA' filled in where no data if available (i.e. for a 3-arm trial, columns for treatments 4 to 6 data will be assigned 'NAs', etc.)

ii) Load the treatment labels from the Excel 'treatment labels' spreadsheet labelled '3-treatment data (Orlistat, Sibutramine, Placebo)' by copying and pasting it into the second box on *MetaInsight*.

*Question: Most studies only have 2-arms, but three studies have 3-arms. Which are the 3-arm studies?*

**Answer: *Aydin 2004, Kaya 2004, Kiortsis 2008***

iii) Click on 'Continuous meta-analysis' and you will see a plot of the individual study results grouped by treatment comparisons. Observe how the 3-arm studies appear in each of the different treatment comparisons.



Individual study results (for all studies) grouped by treatment comparison
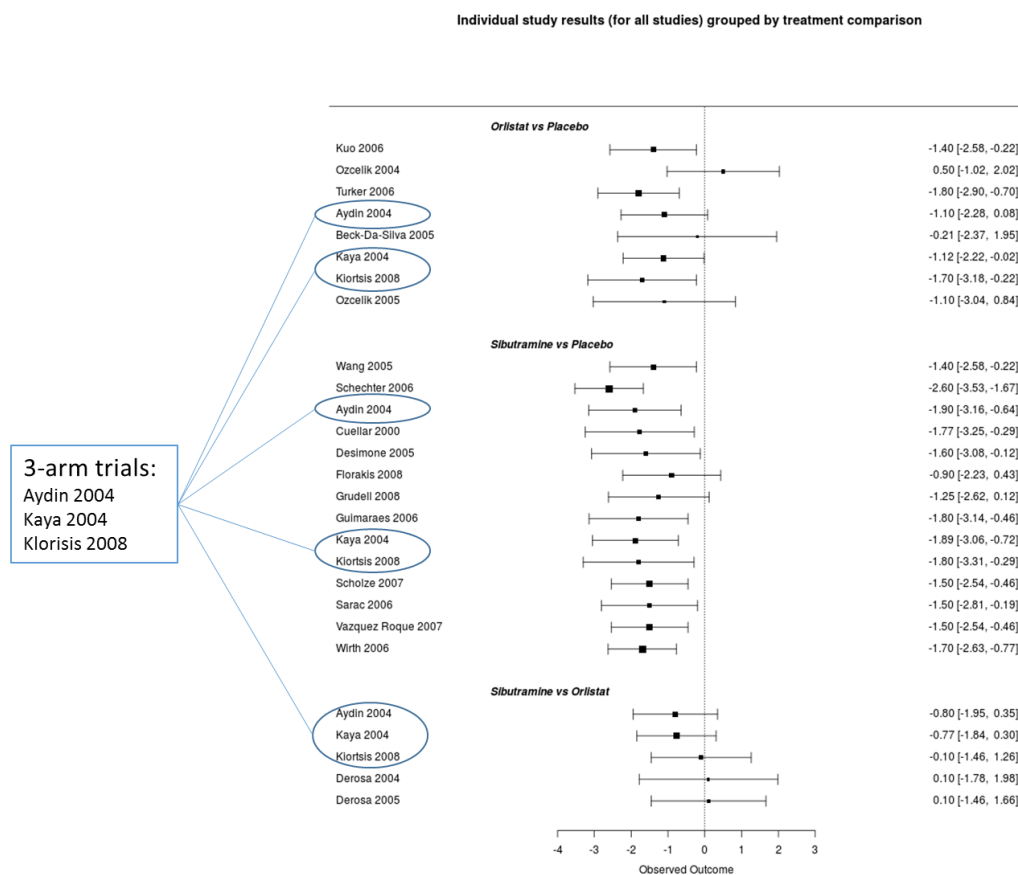
*Question: What conclusions would you make from observing this plot?*

***Answer: All studies consistently favoured Sibutramine to be more effective than Placebo, and the majority of studies favoured Orlistat to be more effective than Placebo with varying degrees of uncertainty. Two out of the five studies favoured Sibutramine when compared to Orlistat and the rest showed no difference in effectiveness between the two active treatments.***

iv) Click on the 'Network Plot' tab and you will see a network diagram displaying the 3 treatments included in the analysis together with the numbers along the lines indicating the number of trial comparisons for treatments defined at either end of the line.  For example, there are 5 pairs of trial arms comparing Orlistat and Sibutramine, which agree with the plot of individual study results presented on the 'Study Results' tab (Note that the shading indicates that there are one or more 3-arm studies).



**Network plot of all studies**
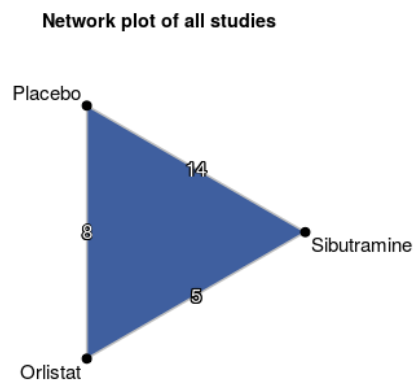
v) The results of the Network Meta-analysis can be observed by clicking on the 'Comparison Plot' tab where the results are presented for each treatment compared to Placebo.

*Question: Interpret the results*
***Answer: Both Orlistat and Sibutramine are more effective at reducing weight than Placebo at the 5% significance level (i.e. the 95% confidence intervals are below zero). In the current version of the App, if you were interested in the comparison of Orlistat and Sibutramine then you would have to re-enter the data in the App with either Orlistat or Sibutramine labelled as treatment 1 (we hope to update this in future versions to enable all comparisons to be obtained).***

**Results for all studies**

| Treatment | Random Effects Model | MD | 95%-CI |
|---|---|---|---|
| Orlistat | | -1.20 | [-1.56; -0.84] |
| Placebo | | 0.00 | |
| Sibutramine | | -1.67 | [-1.93; -1.41] |

-1.5 -1 -0.5 0 0.5 1 1.5
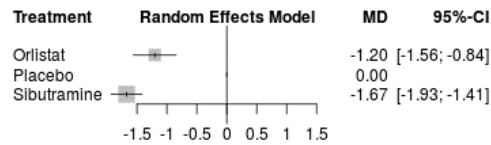
vi) We can also rank the treatments according to their effectiveness and clicking on the 'Rank Chart' tab will present the treatments ranked from 1 (estimated most effective) to 3 (estimated least effective). Caution needs to be applied since there may be considerable uncertainty in these rankings.
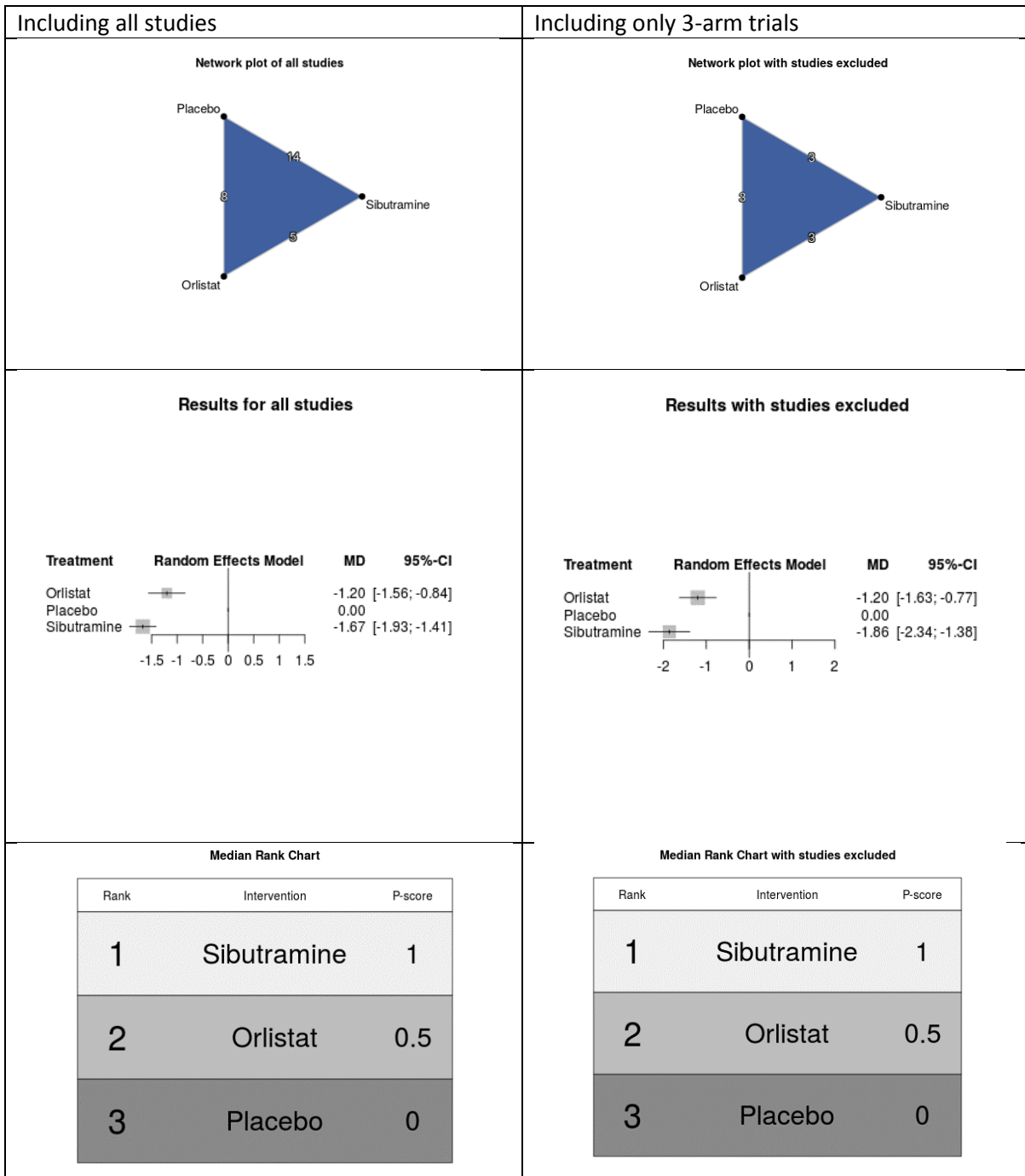
**Median Rank Chart**

| Rank | Intervention | P-score |
|---|---|---|
| 1 | Sibutramine | 1 |
| 2 | Orlistat | 0.5 |
| 3 | Placebo | 0 |

vii) It is easy to exclude studies in *MetaInsight* and to examine the influence this has on the overall results of the network meta-analysis. On the left-hand-side of the screen is a list of all the studies loaded into the App with radial buttons to select those studies you may want to exclude in a sensitivity analysis.

*Question: Keeping only the 3-arm trials (i.e. those studies comparing the 3 treatments of interest directly), observe how the results presented on the following tabs change: 'Network Plot', 'Comparison Plot' and 'Rank Chart'*
***Answer: Despite removing 18 of the 21 studies from the analysis, the results are similar leading to similar conclusions regarding the most effective treatment.***

| Including all studies | Including only 3-arm trials |
|---|---|
| **Network plot of all studies** | **Network plot with studies excluded** |
| Placebo · · Sibutramine · Orlistat (14, 8, 5) | Placebo · · Sibutramine · Orlistat (3, 3, 3) |
| **Results for all studies** | **Results with studies excluded** |
| Treatment · Random Effects Model · MD · 95%-CI | Treatment · Random Effects Model · MD · 95%-CI |

**Results for all studies**

| Treatment | Random Effects Model | MD | 95%-CI |
|---|---|---|---|
| Orlistat | | -1.20 | [-1.56; -0.84] |
| Placebo | | 0.00 | |
| Sibutramine | | -1.67 | [-1.93; -1.41] |

-1.5 -1 -0.5 0 0.5 1 1.5

**Results with studies excluded**

| Treatment | Random Effects Model | MD | 95%-CI |
|---|---|---|---|
| Orlistat | | -1.20 | [-1.63; -0.77] |
| Placebo | | 0.00 | |
| Sibutramine | | -1.86 | [-2.34; -1.38] |

-2 -1 0 1 2

**Median Rank Chart**

| Rank | Intervention | P-score |
|---|---|---|
| 1 | Sibutramine | 1 |
| 2 | Orlistat | 0.5 |
| 3 | Placebo | 0 |

**Median Rank Chart with studies excluded**

| Rank | Intervention | P-score |
|---|---|---|
| 1 | Sibutramine | 1 |
| 2 | Orlistat | 0.5 |
| 3 | Placebo | 0 |

## PART TWO:

In Part One, we kept the analysis simple by including only comparisons between the main three treatments of interest – Orlistat, Sibutramine and Placebo. We are now going to include:

- Further arms for 2 of the studies included in the simplified analysis that administered different treatments
- Further studies that compare additional treatments but connect to the network

i) Create the new dataset in a new Excel spreadsheet by
   a. Copying the original dataset
   b. Replacing the data for Guimaraes 2006 and Kaya 2004 now including all the study arms (new arms highlighted in red)
   c. Adding the 3 additional studies (Borges 2007, Sari 2004, Sathuapalan 2008) at the end of the dataset

ii) Copy and paste the new dataset from Excel into *MetaInsight* (as outlined in Part One) together with the expanded treatment labels.

iii) Note the new comparisons included in the 'Study Results' tab and observe the new network displayed in the 'Network Plot' tab. In particular, it is important to confirm that all the new treatments connect into the network.

*Question: Interpret the results on the 'comparison plot' tab. Is a different treatment now estimated to be the most effective?*

***Answer: All active treatments are estimated to be more effective than placebo. Rimonbant is estimated to be the most effective treatment despite the relatively small amount of evidence (1 trial) and correspondingly uncertain treatment effect estimate. Caution is required when interpreting ranks as it does not take uncertainty into account.***