

# Novel presentational approaches for reporting network meta-analysis

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## Abstract

**Objectives:** To present graphical tools for reporting Network Meta-Analysis (NMA) results aiming to increase the accessibility, transparency, interpretability and acceptability of NMA analyses.

**Study Design and Setting:** Key components of NMA results were identified based on recommendations by agencies such as the National Institute for Health and Care Excellence (UK). Three novel graphs were designed to amalgamate the identified components using familiar graphical tools such as the bar, line or pie charts and adhering to good graphical design principles.

**Results:** Three key components for presentation of NMA results were identified: relative effects and their uncertainty, probability of an intervention being best, and between-study heterogeneity. Two of the 3 graphs developed present results (for each pairwise comparison of interventions in the network) obtained from both NMA and standard pairwise meta-analysis for easy comparison. They also include options to display the probability best, ranking statistics, heterogeneity and prediction intervals. The third graph presents rankings of interventions in terms of their effectiveness to enable clinicians to easily identify “top-ranking” interventions.

**Conclusions:** The graphical tools presented can display results tailored to the research question of interest, and targeted at a whole spectrum of users from the technical analyst to the non-technical clinician.

**Keywords:** Network Meta-Analysis; Graphical displays

**Running title:** Novel presentational approaches for reporting NMA

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**What is new?**

- Network meta-analyses (NMA) generate large amounts of outputs that make reporting of key results challenging, leading to variable reporting styles and often sub-optimal reporting of the results
- Three graphical tools are proposed: two reporting the key results of NMA (alongside pairwise meta-analysis results), whilst the third summarises the overall ranking of the interventions in terms of effectiveness.
- These graphical tools are designed to be tailored to display results relevant to the research question of interest and the different formats are aimed to target both analysts and clinicians.
- Standardising graphical tools for presenting NMA results would increase the acceptability, accessibility, transparency and interpretability of NMA analyses.
- Software for the implementation of the graphical tools are freely available.

## 1 Introduction

Until recently, systematic reviews and health technology assessments (HTA) have been limited to pairwise comparisons of interventions where direct evidence exists. However, often there is an array of candidate interventions relevant to the clinical question of interest, thus an analysis comparing all the relevant interventions may be more appropriate and useful to decision-makers. Methodology to address this issue, which has increasingly been applied, is network meta-analysis (NMA) (also known as mixed (or multiple) treatment comparisons)<sup>1-4</sup>. Despite the increase in the use of NMA, there is no established graphical presentational standard for reporting the results of NMA analogous to the forest plot<sup>5</sup> for meta-analysis<sup>6, 7</sup>.

Here we propose 3 novel graphical tools that aim to present NMA results in a clear and concise manner that combine both graphs and numerical estimates for optimal interpretation of NMA results and with built-in alternative display options to satisfy the needs of different audiences. General principles of graphical excellence for presenting data<sup>8-10</sup>, in a manner that highlight and organise the data effectively, were utilised including reducing non-data ink and enhancing data ink and grouping, prioritising and sequencing the data.

## 2 What is Network Meta-Analysis?

NMA is a recent development in evidence synthesis that extends the functionality of standard pairwise meta-analysis (PWMA) to allow for a simultaneous and coherent comparison of multiple interventions using an evidence base of trials that individually may not compare all the treatment options of interest. Advantages of NMA include: i) preservation of within-trial randomisation when combining Randomised Controlled Trials(RCT) evidence (i.e. NMA is performed using the relative effectiveness results of randomised arms of interventions from each trial included in the network – hence there is no breaking of randomisation when synthesising the results), ii) transparency of the framework (i.e. no need for ‘back of the envelope’ indirect comparisons based on a series of PWMA), and iii) potential reduction of uncertainty due to the inclusion of more data.

Due to the inherent feature of NMA to compare multiple interventions simultaneously, there has been rapid growth in the number of published clinical papers that utilise NMA for the synthesis of evidence from clinical trials, as well as, tutorial articles that focus on educating clinicians and methodologists alike on the fundamentals of NMA and how to interpret NMA results presented in journal articles. For example Salanti<sup>11</sup> summarises what the principles of NMA are, and its benefits and concerns as a next generation evidence synthesis tool. Other tutorial articles with greater relevance to clinicians on understanding the core concepts of NMA, interpreting results from published NMA and hence applying it to real-life clinical situation were published recently in medical journals, for example, by Mills et. al.<sup>12, 13</sup> and Cipriani et. al.<sup>14</sup>.

Given the many advantages and the increased accessibility by the publication of the tutorials, the popularity and use of NMA have increased. However, NMAs generate large numbers of results compared to PWMA; for example a NMA including 5 different treatment regimens generates 10 pairwise comparisons; and this increases to 45 pairwise comparisons when 10 different treatment regimens are included. Presenting such large numbers of results can be challenging, especially when NMA is used to evaluate a number of different outcome measures within the area of interest. Two recent reviews on the reporting of NMA results highlighted the variability in reporting styles<sup>7, 15</sup> in terms of both the content (e.g., relative effect estimates, the probability that a treatment is most effective compared to all other treatments included in the network analysis (referred to subsequently as probability best), etc.) and presentational form (e.g., table, text, graph), and called for additional guidance and presentation tools for reporting NMA results to aid ease of interpretability.

### **3 What NMA results are important?**

A recent review by Tan et al.<sup>7</sup> on the reporting of NMA results in UK National Institute for Health Research (NIHR) HTA reports found that the most often reported NMA results included relative effects of comparative pairs of interventions, absolute effects of interventions, and probability best; all of which are recommended in the published NMA methods guidance documents by agencies such as

the National Institute for Health and Care Excellence (NICE)<sup>16</sup> or International Society For Pharmacoeconomics and Outcomes Research (ISPOR)<sup>17, 18</sup>. Another statistic used in the reporting of NMAs, although not reported in the HTA reports reviewed, is the order of preference of an intervention among a number of interventions (i.e., the ranking of an intervention, where the probability that an intervention is rank 1 is the probability best statistic). The ranks may be presented as summary statistics (e.g., mean/median rank, surface under the cumulative ranking curve(SUCRA)<sup>19</sup>), or graphical representations of the distribution of ranks (e.g. rankograms / barplots) indicating the probability that a given intervention is 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> best, etc. when compared to all other interventions in the network. In addition to the above, PWMA results are reported in the HTA reports, sometimes alongside NMA results to allow informal consistency checks to be made. Prediction intervals (the interval indicating the likely location for the underlying effect in a new study), although not routinely reported, have recently been advocated<sup>20</sup> for the reporting of the impact of heterogeneity in evidence synthesis.

## 4 Data Set

As an illustrative example to present the graphical tools developed, we selected a recently published study that used NMA to investigate the use of tocolytic therapy for preterm child delivery<sup>21</sup>. This published NMA included 95 randomised controlled trials and considered 8 classes of drugs for the treatment of preterm delivery (See Figure 2 of Haas et al<sup>21</sup> for the network of interventions and trials included in the NMA). The primary outcome measurement was 48hr delay in delivery and the analysis was performed on the odds ratio scale. Other secondary outcomes were also analysed in the study but for the illustration of the graphs proposed in this paper, only the results of the primary outcome measure will be displayed; the graphs for the other outcomes will have a similar display format.

In the original article<sup>21</sup>, key analysis results of the primary endpoint, such as NMA and PWMA odds ratios, probability best and rankogram were presented separately using tables and figures (Table 1,

Figure 3 and Figure 7 in the original article – also reproduced in Appendix 2 of this article). The graphical tools proposed here are designed to consolidate the key results into a single figure that enable easier referencing of results for the authors and ease of interpretation of the results for clinicians and academics.

## 5 Graphical tools

In this section three graphical tools are presented that aim to amalgamate the important NMA results, identified in Section 3, to aid readability and maximise interpretation in NMA reports. Two of the graphs present relative effects of comparative pairs of interventions, probability best, ranking statistics (using optionally either rankogram or SUCRA percentages), and heterogeneity estimates. They also present the results of the PWMA alongside the NMA results to allow informal checks for consistency of results to be made easily. The primary aim of the third plot was to give a simple summary of the order of preference of interventions in terms of effectiveness.

The different graphical displays were developed with different target audiences in mind. With academics and statisticians/analysts in mind, the main objective was to graphically present all key NMA results on a single graph whilst ensuring interpretability through clear presentation; this also aimed to help meet restrictions on the number of tables and figures often enforced by research journals (using graphs 1 and 2 below). While completeness of NMA results presentation may be desired by the academics and analysts, clinicians and decision makers in healthcare are more likely to be interested in visualising the overall conclusions of the analysis by presenting the rankings of all interventions in terms of their effectiveness (i.e. highlighting “top-ranking” interventions) (graph 3).

### 5.1 *Graph 1: Summary Forest Plot Matrix (SFP Matrix)*

#### 5.1.1 *Description*

The first plot, referred to as the Summary Forest Plot Matrix, is shown in Figure 1. The plot design is similar to a scatterplot matrix often used for the investigations of correlations. Along the diagonals,



the interventions included in the network are displayed. These interventions may be ordered, for example, by their median rank, as is done here, to highlight the most relevant comparisons by placing them at the top of the graph. Below the diagonal, in the lower triangle of the plot, summary forest plots for all possible combinations of the intervention pairs analysed in the NMA - in black colour - are presented above the PWMA results - in grey colour - to aid visual assessment of consistency between the two analyses (the intervention labelled horizontally to the right of the plot is compared with the intervention labelled vertically above and clear labelling of the axes is given for each 'plot element' on the bottom of the Matrix). The summary forest plots display the point estimates of effect size (drawn as a square) with 95% confidence/credible intervals and 95% prediction intervals (shown by two-tiered error bars). Any summary plot without a grey-coloured estimate indicates a comparison for which no head-to-head trials exist. The corresponding numerical estimates of comparative effectiveness are presented above the diagonal in the upper triangle and are presented as a "mirror image" to the summary forest plots taking the diagonal as the mirror-line. To assist in understanding the heterogeneity of the studies in the network, the numerical estimate of between-study variance (i.e. heterogeneity) is reported below the matrix. Alternating shadings of each plot element is used to improve readability (a technique often used in rail/bus timetables). Also included in the matrix, along the diagonal, are the median ranks together with rankograms which provide the full probability distribution of rankings for each intervention.

For the example in Figure 1, the drug class of prostaglandin inhibitors (row 1) is most likely the best intervention with the highest median rank (1) and probability best statistic as shown on the rankogram (0.80 - the height of the density at rank 1 (x-axis)). Its effectiveness relative to the interventions which are ranked 2<sup>nd</sup> and 3<sup>rd</sup> based on median rank (Magnesium sulfate and Calcium channel blockers) is given by the odds ratio of 0.53 (95% CrI: 0.24 to 1.20) and 0.51 (95% CrI: 0.20 to 1.50) respectively. The lower triangle of the SFP matrix allows the reader to easily identify pairs of interventions for which there were no head-to-head trials. In the example presented in Figure 1, the drug class of prostaglandin inhibitors is compared directly, in head-to-head trials, with all interventions except for the drug classes: others, oxytocin receptor blockers and nitrates (as indicated by the lack of PWMA

estimate below the NMA estimate). This graph allows readers/clinicians to interpret key results of a NMA using a single plot, to compare the NMA and PWMA results and to identify which pairs of interventions could not be compared in a PWMA (due to a lack of head-to-head trials). These functionalities, together with the predictive intervals presented in the graphs could be used to guide potential areas of future clinical trials/epidemiological research studies.

### *5.1.2 Advantages and Limitations*

Traditional forest plots display individual study effects together with the summary estimates to enable readers to assess the effects of each study, how different they are from one another and from the summary estimates, as well as their influence on the summary estimates. As much as it is desirable to display individual studies used in a NMA, it is cumbersome as the number of studies included in a NMA can often be large. Instead the graphical tools developed aimed to use the traditional forest plots, familiar to a great number of audiences in the medical area, to display the summary estimates from both NMA and PWMA and placing them side-by-side. The deliberate placement of the PWMA alongside the NMA results is to allow clinicians to directly address the question that naturally arises with NMA, that is, how different the results of NMA (that uses a network of trials) are compared to the results of traditional PWMA of head-to-head trials.

Along the diagonal, key NMA summary statistics (such as the median ranks together with rankograms which provide the full probability distribution of rankings for each intervention) which are commonly reported separately are included in the graph. By including these statistics on the same plot as the relative effects, it enables the reader to instantly identify which intervention is most likely to be the best and read its comparative effects with all the other remaining interventions (ordering on the median rank statistics further facilitates this by ensuring the “best” interventions are placed at the top of the plot).

Due to the matrix square design of the SFP Matrix, we believe that it works best for networks that are of moderate size ( $< 10$  interventions). Displaying NMA results of larger network will evidently require the SFP matrix to be separated into pages in the multiples of 2, hence reducing the readability and ease of interpretation of the NMA results. As such, we have included options to sort in terms of

key NMA summary statistics and print a user-specified range of interventions which will be discussed in greater details in the display options section.

### *5.1.3 Display Options*

The SFP Matrix shown in Figure 1 is one variant of the many that can be displayed. In its simplest form, the SPF Matrix contains only the NMA and PWMA summary forest plots and estimates (with 95% credible interval), with only the treatment names displayed along the diagonal and the heterogeneity estimates presented. Predictive intervals as shown in Figure 1 can be optionally included in the graph. Further NMA results components such as the ranking statistics and probability a treatment is best can be optionally included in the graph and displayed along the diagonal as shown in Figure 1 where the rankograms were displayed. Ranking statistics can be displayed in the form of (i) rankogram with median rank, (ii) bar chart with mean rank or (iii) the SUCRA estimates with cumulative ranking probability plots. Probability a treatment is best will be displayed with a pie chart with the probability estimates.

Apart from the display of key NMA results components, options to sort or reduce the number of interventions displayed in the graphs are available (with caution notes displayed as footnotes in the graphs to remind readers of the actual number of interventions used in the NMA to produce the displayed results). Although we recommend the presentation of all pairwise comparisons in the network, we also acknowledge that it is sometimes necessary to display a reduced set of interventions, especially in the case of large networks. It may be helpful to clinicians and decision makers to restrict presentation of the NMA results to that of the top 5 or 10 ranking interventions when that the network contains say 20 interventions or more. The NMA components that can be used for sorting the results are (i) median rank; (ii) mean rank; (iii) SUCRA percentages; (iv) probability a treatment is best and (v) relative treatment effect compared to the treatment coded as 1 (which is commonly placebo or standard of care) in the analysis. Footnotes in the graphs can also be removed where it is necessary. Illustrative examples of SFP Matrix plots in its simplest format and with SUCRA percentages are shown in Appendix 1.

## 5.2 Graph 2: Summary Forest Plot Table (SFP Table)

### 5.2.1 Description

The second graph, referred to as the Summary Forest Plot Table, is shown in Figure 2. This plot uses the presentational style of the traditional forest plot where the numerical estimates are reported alongside the summary forest plots. The SFP Table presents results for all possible combinations of intervention comparisons with each intervention in the second column compared to the intervention listed in the first column. Similar to the SFP Matrix above, the interventions have been ordered by their median rank. The third column reports the number of head-to-head trials that compare the two interventions listed in columns 1 and 2 (a feature not incorporated in the SFP Matrix). In column 4 the numerical estimates of the relative effects with corresponding 95% credible interval are presented for the NMA with the PWMA results directly below in grey. Finally, column 5 presents the summary forest plots; again the PWMA results are presented below the NMA results to allow visual assessment of consistency between the two analyses. Similar to the SFP Matrix, the display of the predictive intervals alongside the credible intervals on the summary forest plot is optional. An estimate of heterogeneity across the trials included in the network is also presented. Median ranks of all interventions are also reported in this graph, numerically and graphically using a slider bar format (full rankograms, as presented on the SFP Matrix, were problematic for the SFP Table and difficult to read).

### 5.2.2 Advantages and Limitations

One advantage of this plot over the Matrix format is that the reference line of the summary forest plots for all pairwise comparisons is drawn on the same vertical line, hence facilitating the assessment of differences in comparative estimates and their precision between treatment pairs. Another advantage of this reporting style is that the NMA results from large networks can be reported more easily with the SFP Table extending to multiple pages, where necessary.

Key NMA summary statistics such as the median rank, mean rank, SUCRA percentages and probability best statistics are presented in the top first box of NMA results. This is a result of the

reduction in comparative pairs by one as the primary comparator moves to the next intervention in the NMA. As such for a NMA with 8 interventions (like in our example data), there will only be 7 boxes on the SFP Table because the last intervention (in our example – Placebo) would have been compared to all preceding interventions and will not be listed in column 1 (the primary comparator column). Besides not having the last intervention in column 1, the size of the boxes decreases as it moves towards the next intervention, making it challenging to include rankograms on the graph. This is a limitation of this graph design but is also an advantage of this graph as the key NMA summary statistics had to be placed in the top box and this, in turn, allows readers to compare the interventions without having to flip through pages of the table when the network is large.

### 5.2.3 *Display Options*

The SFP Table shown in Figure 2 is one variant of the many that can be displayed. In its simplest form, the SFP Table contains only the NMA and PWMA summary forest plots and estimates (with 95% credible interval), and the number of head-to-head trials for each pair of intervention comparisons. Predictive intervals as shown in Figure 2 can be optionally included in the graph. Other NMA results components such as the ranking statistics and probability best can be optionally included in the graph and displayed in the first set of intervention comparisons as shown in Figure 2 where the median ranks were displayed. Choice of display of the ranking statistics are (i) median rank presented using slider bar, (ii) mean rank presented using slider bar and (iii) SUCRA percentages. Probability a treatment is best is displayed with a pie chart alongside the probability estimates.

Similar to SFP Matrix, options to sort or reduce the number of interventions displayed in the graphs are available (with caution notes displayed). NMA results components that can be used for sorting the results are (i) median rank; (ii) mean rank; (iii) SUCRA percentages; (iv) probability a treatment is best and (v) relative treatment effect compared to the treatment coded as 1 (which is commonly placebo or standard of care) in the analysis. Illustrative examples of SFP Table plots in its simplest format and with SUCRA percentages are shown in Appendix 1.

### 5.3 Graph 3: Median Rank Chart

#### 5.3.1 Description

The third graph, shown in Figure 3, presents the median ranks of all interventions included in the NMA with the aim to ‘simplify’ the presentation of rankings in NMA. A colour intensity scheme is employed in this graph to help draw attention to the best treatment(s) (using black ink in the lightest zone at the top of the chart) while simultaneously highlight the worst treatment(s) (in the darkest zone at the bottom of the chart). In our example (Figure 3), prostaglandin inhibitors are most likely to be the best with a median rank of 1, while nitrates and placebo are the worst, and the five other interventions have similar rankings between these extremes.

#### 5.3.2 Advantages and Limitations

As this graph allows all interventions included in the NMA to be presented in a single graph that can be printed on a single page, we believe that it is a particularly useful graphical tool when the network contains a large number of interventions. This graph provides readers with only the median ranking of the interventions; hence unlike the SFP Matrix and SFP Table, this does not provide quantitative information on the differences in efficacy estimates between the interventions included in the analysis.

## 6 Software

Functions for creating the graphs in the form presented in this paper have been written in R. The software developed and described in this paper is available from the authors’ departmental website (*to be made available on being accepted*).

## 7 Discussion

In this paper, we have presented 3 graphical tools to aid clear presentation and facilitate interpretation of NMA results. SFP Matrix and SFP Table provide a comprehensive presentation of the important NMA and PWMA results displayed on a single plot. These plots not only enable easy comparison of NMA and PWMA results but also assist to reduce the number of tables and/or figures required for all relevant results to be presented in the main text of a journal article where space is often limited. The Median Rank Chart complements the SFP Matrix or the SFP Table by providing a visual summary of each intervention's median ranking within the network of interest; thus enabling decision makers to easily identify the “top-ranking” intervention(s) in terms of effectiveness. The graphs have been developed to display relative effectiveness results and are reported here on the odds ratio scale, however they can also be used to present other outcome measures (such as continuous, hazard ratios, etc.). An example of its use for the presentation of NMA results on continuous outcome data is shown in Appendix 3.

Visual design principles were applied in the development of the graphs. NMA results presented in the SFP Matrix and SFP Table combine 3 main groups of results, namely (i) the summary forest plot graphs; (ii) the numerical estimates corresponding to the summary forest plots; and (iii) the ranking or probability best statistics. In the SFP Matrix, the most important intervention (e.g. Usual Care/Placebo or the top-ranking intervention when sorted by ranking) is usually at the top left-hand corner and hence the numerical estimates were strategically placed in the upper triangle of the matrix plot. This allows readers to read the relative effectiveness of interventions compared to the most important intervention easily as reading from left to right is generally the order that readers will scan a page. This therefore allows the summary forest plots to be placed in the lower triangle where the x-axis for the plots can be placed at the bottom of the matrix which is conventional with the usual placement of the x-axis on graphs. The ranking or probability best statistics are placed along the diagonal with the intervention names in an enclosure so that readers can readily know what intervention the statistics correspond to. NMA and PWMA results are grouped and placed in an enclosure to allow the assessment of consistency of the results.

In the SFP Table, the three main groups of data are presented from left to right. Firstly, the intervention names together with the ranking or probability best statistics; secondly, the numerical estimates of the relative effectiveness and lastly the summary forest plots. In this design, the texts help to complement and enhance the summary forest plots that follow. Enclosures in the form of boxes present NMA results grouped by the reference intervention, allowing readers to easily recognise that all summary forest plots and numerical estimates within an enclosure are compared to the same reference intervention.

As both the graphs are developed for the presentation of NMA results, the NMA summary forest plots and numerical estimates are presented in stronger (black) ink to highlight the main results while the PWMA results in lighter (grey) ink, displayed for comparison. The intensity of the colours of the enclosures and axes, that do not represent the key results, are reduced to a minimum while light intermittent shading of enclosures in the SFP Matrix is employed to improve readability.

The Median Rank Chart presents the top-ranking intervention at the top, utilising the concept that readers will read from top to bottom, so attention is drawn to the top-ranking intervention first. Also, the top-ranking intervention is written in black ink in the lightest background shading compared to the worse intervention in the darkest background shading, utilising the visual perception concept of contrast to highlight the most important result<sup>9</sup>.

There has been an evolution of reporting standards initially for PWMA<sup>22</sup> and more recently for NMA<sup>17, 18</sup>. Further, Technical Support Documents<sup>23-27</sup>, commissioned by NICE, have recently been published providing technical details of the implications and implementation of NMA methodology as well as guidance on reporting. These all highlight the need for a clear description of the NMA statistical model, and its assumptions, together with model fit statistics, including checks for inconsistency. Additionally, presentation of the evidence structure, in the form of a network diagram<sup>28</sup>, is also recommended. We believe the graphical tools presented in our paper improve existing methods to report the results of an NMA and as such complement the aforementioned guidance documents. The graphs proposed focussed mainly on the presentation of single outcome but



can potentially be adopted to present multiple outcomes in the future. Ultimately, our hope is that such displays will be recommended in updated guidance published in the future.

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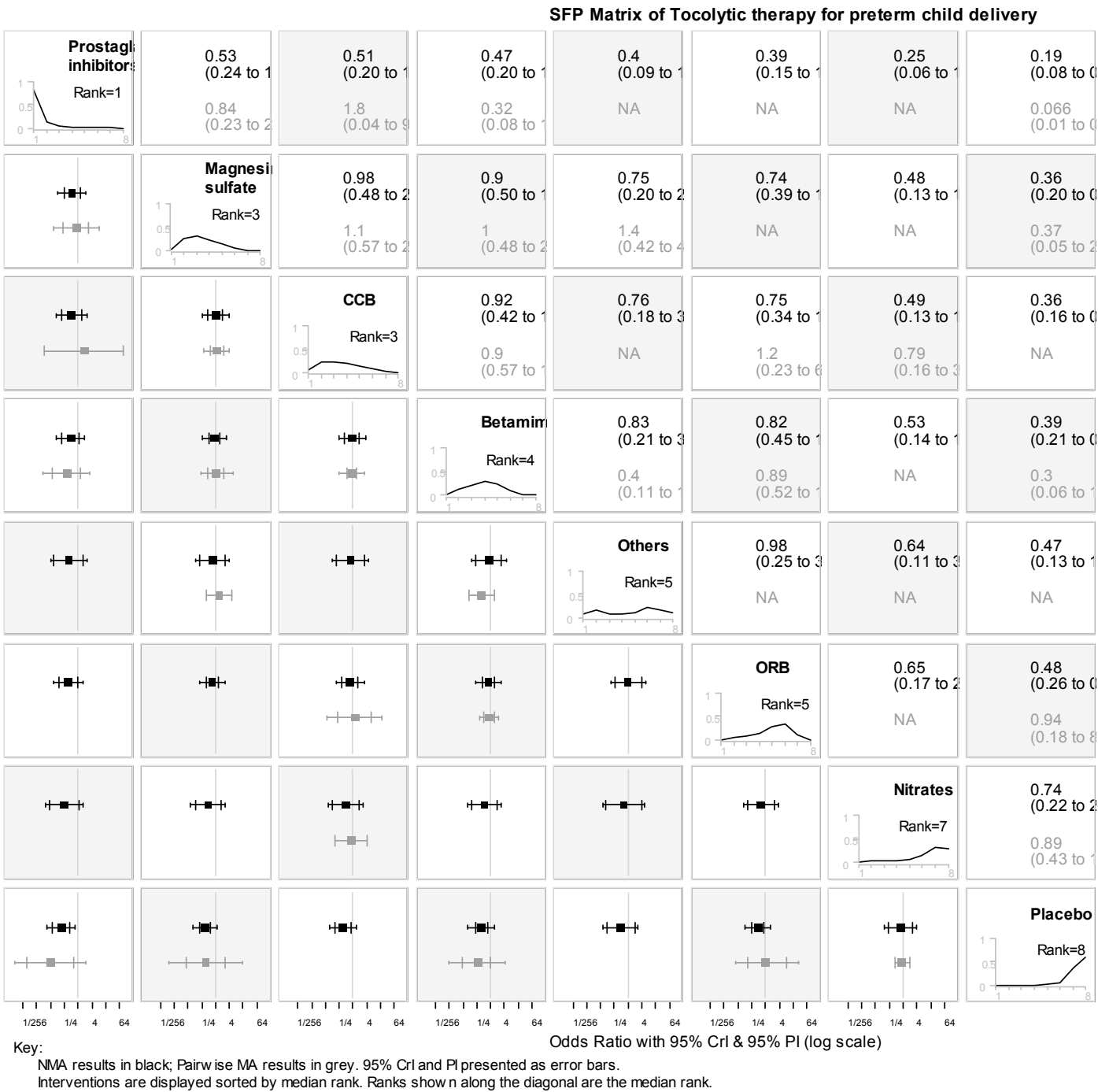


Figure 1: Summary Forest Plot Matrix

SFP Table of Tocolytic therapy for preterm child delivery

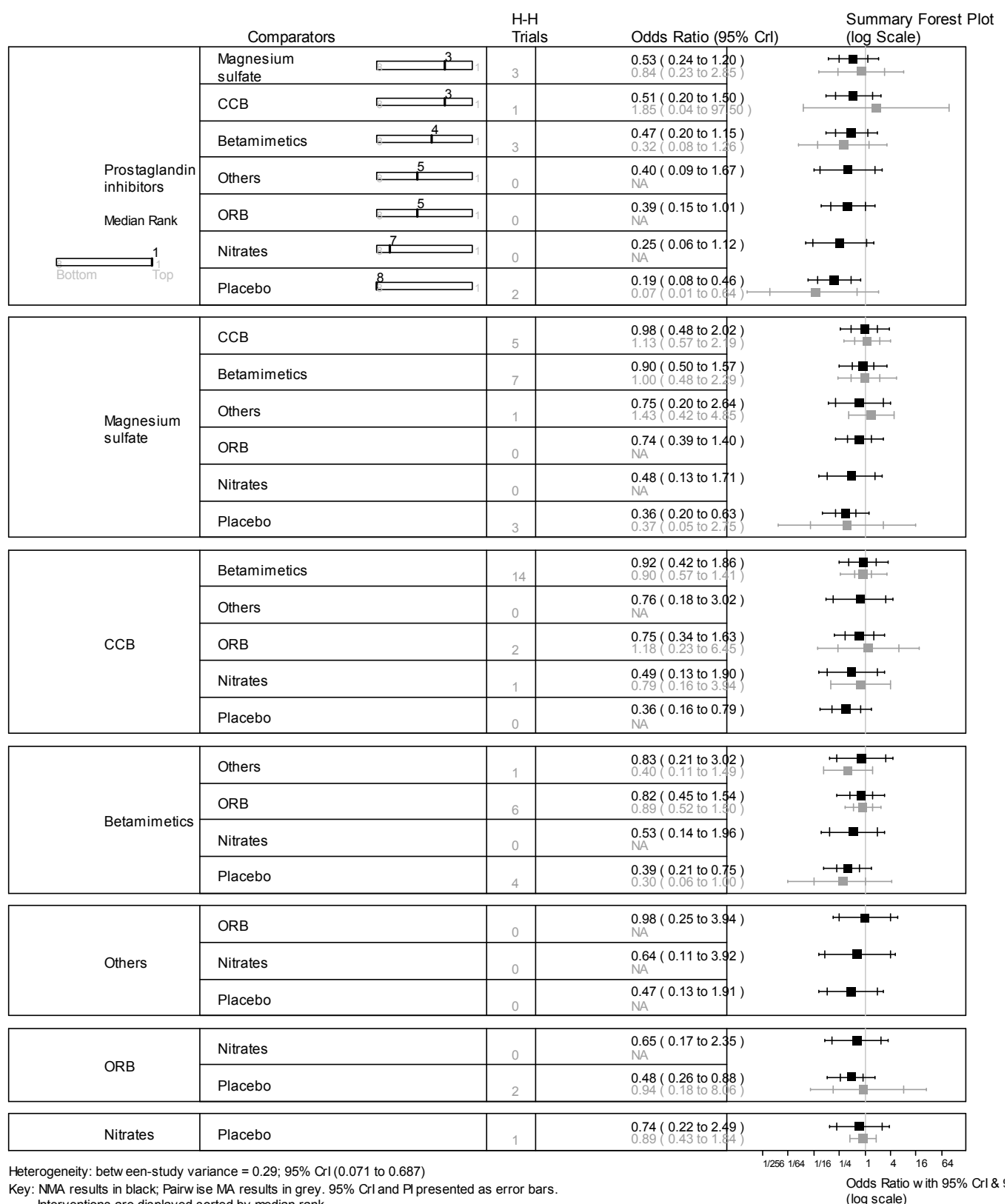


Figure 2: Summary Forest Plot Table

## Median Rank Chart of Tocolytic therapies

Rank	Intervention
1	Prostaglandin inhibitors
2	
3	Calcium channel blockers Magnesium sulfate
4	Betamimetics
5	Others Oxytocin receptor blockers
6	
7	Nitrates
8	Placebo

Figure 3: Median Rank Chart