Interpretation of forest plots – Part I

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At the end of this lecture, you should be able to understand the principles and uses of forest plot. You should also be able to modify the forest plots.
What is a forest plot? Forest plots are graphical representations of the meta-analysis. The word originated from the idea that graph had a forest of lines. The plot originated in the early eighties although the term forest plot was coined only in 1996. Forest plots in their modern form originated in 1998.
What does a forest plot show? Each study represented by a line.

- Each study represented by a line
- Note that Study4 is not represented by a line
  - Zero events in both groups
  - Study excluded from the meta-analysis.

What does a forest plot show? Each study represented by a line. Note that Study4 is not represented by a line since there are no events in either group. Such studies will be excluded from the meta-analysis.
What does a forest plot show?

- Box in the line for each study
  - Mid-point
    - Point effect estimate of each study
  - Area
    - Weight given to the study
- Diamond
  - Overall effect estimate

There is a box in the line for each study. The mid-point of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. This is designed so that eyes are drawn towards the studies that are given more weight. The diamond below the studies represents the overall effect.
The width of the line shows the confidence intervals of the effect estimate of individual studies. The width of the diamond shows the confidence intervals for the overall effect estimate.
What do point estimate and 95% confidence intervals mean?

- **Point estimate**
  - Best guess of the true effect in the population
- **95% confidence intervals**
  - 95% chance that the true effect in the population will lie within the range
  - If trial repeated, 95% chance that the point estimate from the trial lies within the range

What do point estimate and 95% confidence intervals mean? Point estimate is best guess of the true effect in the population. 95% confidence intervals mean that there is a 95% chance that the true effect in the population will lie within the range. They also mean that if the trial is repeated, there is a 95% chance that the point estimate from the trial lies within the 95% confidence intervals obtained in the systematic review. These are based on the sample being representative and the assumption that there are no systematic errors that can bias the results.
The Forest plot also provides the summary data entered for each study. In addition, it provides the weight for each study; the effect measure, method and the model used to perform the meta-analysis; the confidence intervals used; the effect estimate from each study, the overall effect estimate, and the statistical significance of the analysis. For the time being, ignore the information on heterogeneity. This will be explained in the next lecture.
Note the other important information present in the forest plot. There is a vertical line which corresponds to the value 1 in the plot shown. This is the line of no effect. Note also that it says favours experimental to the left of the vertical line and ‘favours control’ to the right of the vertical line. These are called labels of the forest plot. These labels can be edited. Before we learn how to edit the labels, it is necessary to understand what these mean and what labels should be used.
Effect measures

• Binary outcomes
  – Odds ratio
  – Risk ratio
  – Risk difference

• Continuous outcomes
  – Mean difference
  – Standardised mean difference

• Count data outcomes
  – Rate ratio

• Time-to-event outcomes
  – Hazard ratio

This slide is to refresh the different effect measures that are commonly used for different type of outcomes.
All ratios commonly used as effect measures in meta-analyses are relative measures. In this case, 1 indicates no effect. If 1 is included in the 95% confidence intervals, it indicates that there is no statistical significance at 5% significance levels. If 1 is not included in the 95% confidence intervals, the results are statistically significant at 5% significance levels. This is applicable for effect estimates for the individual study level and for the overall estimate. Whether the intervention is beneficial or harmful depends upon the context. The different situations that one faces when calculating ratios is shown in the next few slides.
This slide shows an example of a bad event such as mortality. The 95% confidence intervals of all the studies overlap 1. The 95% confidence intervals of the overall effect estimate also overlaps 1. So, there is no statistical significance either at the study level or the meta-analysis level. Note that for a bad event, the label ‘favours intervention’ is on the left of the line of no effect and the label ‘favours control’ is on the right of the line of no effect.
The 95% confidence intervals of all the studies overlap 1. The 95% confidence intervals of the overall effect estimate does not overlap 1. So, there is no statistical significance at the study level but there is statistical significance at the meta-analysis level. Intervention is better as the overall effect estimate and its 95% confidence intervals are to the left of the line of no effect.
The 95% confidence intervals of all the studies except those of one study overlap 1. The 95% confidence intervals of the overall effect estimate overlaps 1. So, there is no statistical significance at the study level except for the one study. In this study marked with a red ellipse in the slide, the intervention is better than the control. There is no statistical significance at the meta-analysis level.
- **Individual studies**
  - All studies except one study 95% CI overlaps 1
  - No statistical significance except this study

- **Overall effect estimate**
  - 95% CI does not overlap 1
  - Statistical significance

The 95% confidence intervals of all the studies except one study overlap 1. The 95% confidence intervals of the overall effect estimate does not overlap 1. So, there is no statistical significance at the study level except for the one study. There is statistical significance at the meta-analysis level. Intervention is better as the overall effect estimate and its 95% confidence intervals are to the left of the line of no effect.
The 95% confidence intervals of all the studies except one study overlap 1. The 95% confidence intervals of the overall effect estimate does not overlap 1. So, there is no statistical significance at the study level except for the one study. There is statistical significance at the meta-analysis level. Intervention is worse than control as the overall effect estimate and its 95% confidence intervals are to the right of the line of no effect.
Note that for a good event such as early return to work, the label ‘favours intervention’ is on the right of line of no effect and the label ‘favours control’ is on the left of the line. It is important to note that this does not happen automatically and has to be done manually. This will be shown in one of the later slides in this lecture. On the forest plot shown, the 95% confidence intervals of all the studies except one study overlap 1. The 95% confidence intervals of the overall effect estimate does not overlap 1. So, there is no statistical significance at the study level except for the one study. There is statistical significance at the meta-analysis level. Intervention is better than control as the overall effect estimate and its 95% confidence intervals are to the right of the line of no effect.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Events</th>
<th>Control Events</th>
<th>Total Weight</th>
<th>Risk Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>5</td>
<td>10</td>
<td>3.50 [0.19, 30.00]</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>4</td>
<td>10</td>
<td>4.80 [0.60, 30.00]</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>3</td>
<td>20</td>
<td>4.50 [0.50, 40.00]</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>4</td>
<td>10</td>
<td>4.00 [0.47, 34.34]</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>4</td>
<td>10</td>
<td>4.00 [0.47, 34.34]</td>
<td></td>
</tr>
<tr>
<td>Study 6</td>
<td>10</td>
<td>102</td>
<td>4.50 [2.13, 9.49]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 227 240 100.0% 4.50 [2.13, 9.49] 1

Individual studies
- All studies except one study 95% CI overlaps 1
- No statistical significance except this study

Overall effect estimate
- 95% CI does not overlap 1
- Statistical significance
This table summarises the interpretation of forest plot when ratios are used as effect measures.

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Example</th>
<th>Which side of 1 does the label 'favours intervention' lie?</th>
<th>Which side of 1 does the overall estimate and 95% CI lie?</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bad event</td>
<td>Mortality</td>
<td>Left</td>
<td>Left</td>
<td>Favours intervention</td>
</tr>
<tr>
<td>Bad event</td>
<td>Mortality</td>
<td>Left</td>
<td>Right</td>
<td>Favours control</td>
</tr>
<tr>
<td>Good event</td>
<td>Early return to work</td>
<td>Right</td>
<td>Left</td>
<td>Favours control</td>
</tr>
<tr>
<td>Good event</td>
<td>Early return to work</td>
<td>Right</td>
<td>Right</td>
<td>Favours intervention</td>
</tr>
</tbody>
</table>
Differences

- Absolute measures
- All differences
  - 0 indicates no effect
  - If 0 is included in the 95% confidence intervals
    - No statistical significance at 5% significance levels
  - If 0 is not included in the 95% confidence intervals
    - Statistical significance at 5% significance levels
    - Benefit or harm depends upon the context

All differences commonly used as effect measures in meta-analyses are absolute measures. In this case, 0 indicates no effect. If 0 is included in the 95% confidence intervals, it indicates that there is no statistical significance at 5% significance levels. If 0 is not included in the 95% confidence intervals, the results are statistically significant at 5% significance levels. This is applicable for effect estimates for the individual study level and for the overall estimate. Whether the intervention is beneficial or harmful depends upon the context. The different situations that one faces when calculating differences and the interpretation is shown in the next few slide.
This table summarises the interpretation of forest plot when differences are used as effect measures. The interpretation is pretty much the same as for ratios. The only difference is that the line of no effect is at zero for differences while it is at 1 for ratios.
Although a forest plot is generated as soon as you enter the data, a separate forest plot can be generated by clicking on the icon shown.
Generating forest plot

From the resulting window, one can save, copy, or print the forest plot.
Now that the labels for different situations has been explained, it is necessary that you learn to make the changes in forest plots generated by RevMan. Double click the outcome. Click on the cogwheels in right upper region. This opens up a window with which you should be familiar by now. Click on the graph tab.
You can edit the left graph label and the right graph label. You can also add units for mean difference. There are no units for other effect measures.
The point estimates and most, if not all, of the confidence intervals should be visible in the plot. The point estimates should be of reasonable size. This can be done by adjusting the slider, shown as red circle.
Forest plots should not be used when there are no studies reporting the outcome. The Cochrane Collaboration discourages the use of forest plots if there is only one study reporting the outcome.
In this lecture, basic principles of interpretation of forest plots and the way they can be modified was demonstrated. Please complete the exercise in the next slide. Discuss the results of your exercise with your course tutor. If you have any other doubts related to the lecture, please discuss with your course tutor.
Exercise 4-1

• Generate and interpret the forest plots for the different outcomes for the following comparisons
  – Early bathing or showering after surgical wounds
  – HPV Vaccination or no vaccination for prevention of cervical cancer

• Alternatively complete the above task for the topics that you chose for lecture 3 of the previous module.
Exercise 4-2

- Generate and interpret the forest plots for the five examples Example 4-1 to Example 4-5