Planning analysis in a systematic review
Writing analysis section of the protocol

- Which study designs are appropriate to combine?
- What treatment effect measures?
- How to identify and investigate heterogeneity?
- Fixed or random effects or both?
- How to impute missing data?
- How to address publication bias?
Planning the analysis

- **Effect or Rx effect:** The contrast between the outcomes of two groups treated differently.

- What is the direction of effect?

- What is the size of effect?

- Is the effect consistent across studies?

- What is the strength of evidence for the effect?
Reasons for meta-analysis

• To increase power

• To improve precision

• To check consistency or reasons for inconsistency across studies

• To settle controversies

• To generate new hypotheses.
When not to do meta-analysis in a review?

- Poor quality studies
- Different populations
- Different interventions
- Different comparisons
- Different outcomes
Planning analyses : ITT issue

What is ITT?
Includes all trial participants in the assigned groups regardless of what happened subsequently.

Issues:
1. Compliance to the protocol by patients/physicians
2. Losses to follow-up
3. Ineligibility
Available case Analysis

- Includes those with known outcome

- Three types of exclusions
  - Pre-specified, based on pre randomization information
  - Immediate post-randomization before Rx
  - Drop outs: assess potential impact
ITT analysis using imputation

• Dichotomous:
  Worst-case/best-case scenario analysis

• Continuous:
  last observation carried forward

• Imputing 'Zero' QOL for deaths

• (Consider hierarchy of outcomes)
Synthesis: combining

• Taking out average

• A question
Question

• A class has 200 boys and 100 girls

• Average weight: boys (70 kg), girls (40 kg)

• What is the average weight of the class?
Two studies: weight reduction prevents heart attack

• How many years follow up is required?

• Where is it easy to follow up?

• One smart proposal (2000 subjects)

• One conventional proposal
Results of the two studies

• Smart study:
  – weight reduction arm: 1/1000 events
  – Control arm: 2/1000 events

• Conventional study
  – Weight reduction arm: 75/1000 events
  – Control arm: 150/1000 events

Should both studies get equal weight?
Which study should get more weight?
Assigning weight to studies

• Based on quality (less the systematic error, more the weight)

• Based on sample size

• Based on number of outcome events
Dealing with students’ complaint
Students’ union writes to the Dean

• There has been a problem with the examination results

• Some students who failed were actually good

• Some students who passed were not good at all.
Dean appoints a committee

• To examine whether there is really a need to investigate this?

• If so, then investigate the problem.
Overview of the examination

• Written exam: Full marks 100

• Practical: Full marks 100

• Oral (Viva-voce): Full marks 100

• Pass marks: 50% of total overall
# FOUR PATTERNS

<table>
<thead>
<tr>
<th>Parts of exam</th>
<th>Pattern 1</th>
<th>Pattern 2</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written (100)</td>
<td>55</td>
<td>15</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>Practical (100)</td>
<td>60</td>
<td>70</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Oral (viva-voce) (100)</td>
<td>65</td>
<td>80</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Total (300)</td>
<td>180 (60%)</td>
<td>165 (55%)</td>
<td>120 (40%)</td>
<td>135 (45%)</td>
</tr>
</tbody>
</table>
Patterns to investigate

• Patterns 2 and 4
• Why?

• Unacceptable because the marks are dissimilar across the various evaluations.
• Acceptable when the marks are similar.
• Any scientific word (synonym) for similarity?
Acceptability depends on

- similarity across evaluations
- Similarity = homogeneity
- Dissimilarity = heterogeneity
How does it fit with meta-analysis?

• Meta-analysis is a study of studies.
• Nothing but taking out an average from two or more measurements.
• Each study evaluates and measures the effect.
• Summary effect measure is the average.
• Acceptable if there is homogeneity across the studies
• If there is heterogeneity, investigate.
### Pattern 1

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral_a</td>
<td>55</td>
<td>5</td>
<td>33.3%</td>
<td>55.00 [45.20, 64.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practical_a</td>
<td>60</td>
<td>5</td>
<td>33.3%</td>
<td>60.00 [50.20, 69.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written 1010a</td>
<td>65</td>
<td>5</td>
<td>33.3%</td>
<td>65.00 [55.20, 74.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>60.00 [54.34, 65.66]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 20.78 (P < 0.00001)
## PATTERN 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral_a</td>
<td>15</td>
<td>5</td>
<td>33.3%</td>
<td>15.00 [5.20, 24.80]</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>Practical_a</td>
<td>70</td>
<td>5</td>
<td>33.3%</td>
<td>80.00 [70.20, 89.80]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written 1010a</td>
<td>80</td>
<td>5</td>
<td>33.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**  
100.0%  55.00 [49.34, 60.66]

Heterogeneity: Chi² = 98.00, df = 2 (P < 0.00001); I² = 98%

Test for overall effect: Z = 19.05 (P < 0.00001)
### PATTERN 3

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral_a</td>
<td>40</td>
<td>5</td>
<td>33.3%</td>
<td>40.00 [30.20, 49.80]</td>
<td></td>
</tr>
<tr>
<td>Practical_a</td>
<td>45</td>
<td>5</td>
<td>33.3%</td>
<td>45.00 [35.20, 54.80]</td>
<td></td>
</tr>
<tr>
<td>Written 1010a</td>
<td>35</td>
<td>5</td>
<td>33.3%</td>
<td>35.00 [25.20, 44.80]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

100.0% 40.00 [34.34, 45.66]

Heterogeneity: \( \chi^2 = 2.00, \text{df} = 2 (P = 0.37); I^2 = 0\%

Test for overall effect: \( Z = 13.86 (P < 0.00001) \)
### PATTERN 4

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>SE</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral_a</td>
<td>90</td>
<td>5</td>
<td>33.3%</td>
<td>90.00 [80.20, 99.80]</td>
<td></td>
</tr>
<tr>
<td>Practical_a</td>
<td>20</td>
<td>5</td>
<td>33.3%</td>
<td>20.00 [10.20, 29.80]</td>
<td></td>
</tr>
<tr>
<td>Written 1010a</td>
<td>15</td>
<td>5</td>
<td>33.3%</td>
<td>15.00 [5.20, 24.80]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- 100.0% 41.67 [36.01, 47.32]

Heterogeneity: \( \chi^2 = 140.67, \text{df} = 2 \) \( (P < 0.00001) \); \( I^2 = 99\%

Test for overall effect: \( Z = 14.43 \) \( (P < 0.00001) \)
### Corticosteroids for acute bacterial meningitis

**Outcome:** 02 Severe hearing loss

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belsey 1989</td>
<td>0/41</td>
<td>1/42</td>
<td>1.9 [0.01, 8.14]</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Bhaumik 1998</td>
<td>2/13</td>
<td>2/13</td>
<td>2.6 [0.16, 6.07]</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Girgis 1989</td>
<td>2/190</td>
<td>5/177</td>
<td>6.6 [0.07, 1.90]</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Kanra 1995</td>
<td>0/29</td>
<td>0/27</td>
<td></td>
<td>0.0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Kilpi 1995</td>
<td>1/32</td>
<td>3/26</td>
<td>4.2 [0.03, 2.46]</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>King 1994</td>
<td>2/50</td>
<td>3/50</td>
<td>3.8 [0.12, 3.82]</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Lebel 1988a</td>
<td>2/51</td>
<td>9/48</td>
<td>11.9 [0.05, 0.92]</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Lebel 1988b</td>
<td>1/51</td>
<td>6/49</td>
<td>7.9 [0.02, 1.28]</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Lebel 1989</td>
<td>1/31</td>
<td>2/29</td>
<td>2.7 [0.04, 4.89]</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Molyneux 2002</td>
<td>31/181</td>
<td>27/189</td>
<td>33.9 [0.75, 1.93]</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>Odio 1991</td>
<td>3/51</td>
<td>7/48</td>
<td>9.3 [0.11, 1.47]</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Qazi 1996</td>
<td>1/36</td>
<td>1/36</td>
<td>1.3 [0.07, 15.38]</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Schaad 1993</td>
<td>2/60</td>
<td>4/55</td>
<td>5.4 [0.09, 2.40]</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Wald 1995</td>
<td>2/88</td>
<td>7/74</td>
<td>8.6 [0.07, 1.45]</td>
<td>0.31</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 884/883

**Total events:** 50 (Treatment), 77 (Control)

**Test for heterogeneity chi-square:** 13.57 df=12 p=0.33 $I^2=11.8\%$

**Test for overall effect z=2.51 p=0.01**
Review: Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis
Comparison: 01 Third generation cephalosporins versus conventional therapy
Outcome: 01 Death

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>3 g cephalosporins n/N</th>
<th>Conventional n/N</th>
<th>RD (fixed) 95% CI</th>
<th>Weight %</th>
<th>RD (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delrio 1983</td>
<td>0/39</td>
<td>0/39</td>
<td>5.24</td>
<td>0.00</td>
<td>[0.00, 0.00]</td>
</tr>
<tr>
<td>Narciso 1983</td>
<td>0/5</td>
<td>0/5</td>
<td>0.67</td>
<td>0.00</td>
<td>[-0.31, 0.31]</td>
</tr>
<tr>
<td>Steele 1983</td>
<td>0/15</td>
<td>0/15</td>
<td>2.02</td>
<td>0.00</td>
<td>[-0.12, 0.12]</td>
</tr>
<tr>
<td>Aronoff 1984</td>
<td>0/10</td>
<td>0/7</td>
<td>1.11</td>
<td>0.00</td>
<td>[-0.21, 0.21]</td>
</tr>
<tr>
<td>Congeni 1984</td>
<td>2/22</td>
<td>1/23</td>
<td>3.02</td>
<td>0.05</td>
<td>[-0.10, 0.19]</td>
</tr>
<tr>
<td>Wells 1984</td>
<td>0/12</td>
<td>1/18</td>
<td>1.94</td>
<td>-0.06</td>
<td>[-0.22, 0.10]</td>
</tr>
<tr>
<td>Barson 1985</td>
<td>0/27</td>
<td>0/23</td>
<td>3.34</td>
<td>0.00</td>
<td>[0.08, 0.08]</td>
</tr>
<tr>
<td>Bryan 1985</td>
<td>4/18</td>
<td>3/18</td>
<td>2.42</td>
<td>0.06</td>
<td>[-0.20, 0.31]</td>
</tr>
<tr>
<td>Jacobs 1985</td>
<td>0/23</td>
<td>1/27</td>
<td>3.34</td>
<td>-0.04</td>
<td>[-0.14, 0.06]</td>
</tr>
<tr>
<td>Rodriguez 1985</td>
<td>12/61</td>
<td>8/39</td>
<td>6.40</td>
<td>-0.01</td>
<td>[-0.17, 0.15]</td>
</tr>
<tr>
<td>Odio 1986</td>
<td>3/42</td>
<td>3/43</td>
<td>5.71</td>
<td>0.00</td>
<td>[-0.11, 0.11]</td>
</tr>
<tr>
<td>Girgis 1987</td>
<td>1/15</td>
<td>1/15</td>
<td>2.02</td>
<td>0.00</td>
<td>[-0.18, 0.18]</td>
</tr>
<tr>
<td>Girgis 1988</td>
<td>7/50</td>
<td>10/50</td>
<td>6.72</td>
<td>-0.06</td>
<td>[-0.21, 0.09]</td>
</tr>
<tr>
<td>Haffejee 1988</td>
<td>2/16</td>
<td>3/15</td>
<td>2.08</td>
<td>-0.08</td>
<td>[-0.33, 0.18]</td>
</tr>
<tr>
<td>Tuncer 1968</td>
<td>1/20</td>
<td>2/22</td>
<td>2.82</td>
<td>-0.04</td>
<td>[-0.19, 0.11]</td>
</tr>
<tr>
<td>Peltola 1989</td>
<td>5/101</td>
<td>4/99</td>
<td>13.44</td>
<td>0.01</td>
<td>[-0.05, 0.07]</td>
</tr>
<tr>
<td>Filali 1993</td>
<td>1/16</td>
<td>1/20</td>
<td>2.39</td>
<td>0.01</td>
<td>[-0.14, 0.16]</td>
</tr>
<tr>
<td>Sharma 1996</td>
<td>0/11</td>
<td>0/12</td>
<td>1.54</td>
<td>0.00</td>
<td>[-0.15, 0.15]</td>
</tr>
<tr>
<td>Nathan 2005</td>
<td>14/247</td>
<td>12/256</td>
<td>33.79</td>
<td>0.01</td>
<td>[-0.03, 0.02]</td>
</tr>
</tbody>
</table>

Total (95% CI): 750 vs 746
Total events: 52 (3 g cephalosporins), 50 (Conventional)
Test for heterogeneity: Chi² = 3.23, df = 18 (P = 1.00), I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Figure 2. Percentage reduction in risk of ischaemic heart disease (and 95% confidence intervals) associated with 0.6 mmol/l serum cholesterol reduction in 10 prospective studies of men (Thompson 1994)
Take home message

• In a meta-analysis

• Results are acceptable if there is homogeneity

• Need to investigate if there is heterogeneity

• Heterogeneity lowers the level of evidence
Heterogeneity

• Variability among studies

• Three types
  – clinical (different Rx effect)
  – Methodological (different degree of bias)
  – statistical (due to above)

• Apples and oranges are all fruits
Identifying heterogeneity

- Closeness of point estimates
- Overlap of CIs
- Chi-squared test (false negative, false positive)
- \( I^2 = \) quantifies inconsistency.
- \( I^2 = \) percent of variability in effect estimates that is due to heterogeneity.
Addressing heterogeneity

- Check data
- Do not meta-analyse
- Explore heterogeneity (meta-regression)
- Ignore heterogeneity
- Incorporate heterogeneity
- Exclude studies or do sensitivity analysis
WHICH FORMULA TO USE FOR COMBINING?
Fixed vs Random effects model

• Fixed: differences solely due to chance

• Random: do not know why the effects are different (consider as if they were random)

• Normal distribution of effect

• Both co-incide if no heterogeneity

• Random: more weight to small studies and exacerbates publication bias.

• Few small trials – M-H method but ignores heterogeneity.
Sensitivity analyses

• Do results change by different ways of doing the meta-analysis?

• Do not change - 'robust' results

• Do Change - 'sensitive'

• What if change inclusion criteria

• Include / exclude borderline studies

• Change outcomes

• Impute 'missing data' differently

• Random vs fixed effects.
Publication bias

- Positive results are favored for publication
- Investigate using 'funnel plot'
- Scatter plot of Rx effects of individual studies (x-axis) against a measure of sample size (y-axis)

- Symmetrical = no publication bias
- Asymmetry = has many causes
Summary

• Quantitative/mathematical process of combining results from more than one study is meta-analysis.
• Sometimes, not advisable to do meta-analysis.
• To do it select measure of effect (association), model for combining.
• Deal with missing data.
• Investigate heterogeneity, do sensitivity analysis.
Thank You
## RR vs OR

<table>
<thead>
<tr>
<th>Death</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGR/CGR</strong></td>
<td><strong>EGR/CGR</strong></td>
</tr>
<tr>
<td>20%/60%</td>
<td>80%/40%</td>
</tr>
<tr>
<td>RR=1/3</td>
<td>RR=80/40=2</td>
</tr>
<tr>
<td>Odds ratio = ( \frac{1}{4} \times \frac{2}{3} )</td>
<td>RBI = 100%</td>
</tr>
<tr>
<td>RRR=0.66</td>
<td>OR = 4*(3/2)= 6</td>
</tr>
<tr>
<td>OR= 1/6</td>
<td></td>
</tr>
</tbody>
</table>