Using meta-analysis to inform the design of subsequent studies

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Motivating Example

- Systematic review of antibiotic use for common cold from Cochrane database of systematic reviews (1).

- Six trials were conducted to compare antibiotics versus placebo for outcome symptoms persisting beyond 7 days.

- There were a total of 1147 subjects, 664 in the treatment group and 483 in the control group.
Motivating Example

<table>
<thead>
<tr>
<th>Study</th>
<th>Or (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herne (1980)</td>
<td>0.22 (0.07, 0.69)</td>
<td>6.87</td>
</tr>
<tr>
<td>Hoaglund (1950)</td>
<td>0.69 (0.42, 1.13)</td>
<td>38.04</td>
</tr>
<tr>
<td>Kaiser (1996)</td>
<td>1.01 (0.62, 1.65)</td>
<td>38.88</td>
</tr>
<tr>
<td>Lexomboon (1971)</td>
<td>1.00 (0.29, 3.42)</td>
<td>6.15</td>
</tr>
<tr>
<td>McKerrow (1961)</td>
<td>0.63 (0.15, 2.59)</td>
<td>4.61</td>
</tr>
<tr>
<td>Taylor (1977)</td>
<td>1.91 (0.52, 7.06)</td>
<td>5.46</td>
</tr>
<tr>
<td>Overall (I-squared = 38.0%, p = 0.153)</td>
<td>0.80 (0.59, 1.08)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Overall (I-squared = 38.0%, p = 0.153)
Motivating Example

- The review concluded that “there was insufficient evidence of benefit to warrant the use of antibiotics”. Further trials could be potentially beneficial.

- It is possible that additional information in the form of another trial could change this result.
The Concept

- Individual clinical trials or diagnostic accuracy studies rarely provide enough information to make conclusive recommendations.

- Sutton et al. (2) proposed when designing a new trial would be reasonable to consider power of updated meta-analysis including new trial rather than power of new trial itself.

- The subsequent updated meta-analysis would be more influential than results of new study on its own.

- The methods have recently been adapted for diagnostic test accuracy (3).
Power by Simulation

1. A distribution for the effect size expected to be seen in the new study is derived from the M-A of existing evidence. A starting sample size is specified indicating the initial size of the new study considered. Data relating to a new study is generated stochastically.

2. The simulated study is then included in the meta-analysis and a rule used to establish whether the result is “decisive”.

3. Steps 1 and 2 are repeated a large (N) number of times recording whether the result is “decisive or not”.

4. Power is estimated by calculating what proportion of the N simulations are deemed to give “decisive” results.

5. Procedure is iterative using different sample sizes until the desired level of power is achieved.
What is a Decisive Result?

Possible options are:

1. Conventional: statistical significance of pooled effect - say 5% level.

2. Variance minimisation: reduce the variance of the pooled effect to a specified level (irrespective of statistical significance).

3. Limits of equivalence (minimal clinical worthwhile benefit): decisive when pooled effect and (95%) confidence interval lie completely within, or outside, pre-specified limits of equivalence.
Overview of Stata Software

- Collection of three programs to implement the frequentist version of the methodology for (2-arm) randomised controlled trials and diagnostic test accuracy contexts.

1. metasim
2. metapow
3. metapowplot
Overview of Stata Software

**metasim**

- Simulates specified number of new studies based on estimate/s obtained from pre-existing meta-analysis assuming effect size seen in new study will be consistent with existing studies in meta-analysis.

- Program can be used independently, but was designed to be used in conjunction with metapow.
Overview of Stata Software

metapow

- Power is determined through simulation, with data for new studies being generated using program metasim.

- For certain inferences can also estimate power of new study when analysed on its own.
Overview of Stata Software

metapowplot

▶ Produces plot of power values for a range of sample sizes.

▶ Calls on program metapow which in turn calls on metasim.
Software Relationship Diagram

- metapowplot
  - metan
  - metapow
    - metasim
    - metandi
    - midas
  - extfunnel
Using `metapowplot`

```
. metapowplot event_t noevent_t event_c noevent_c, start(100) step(100) stop(1000) type(clinical) measure(or) model(fixedi) nit(100) inference(pvalue) pow(0.05)
```

Sample size

<table>
<thead>
<tr>
<th>t</th>
<th>Treatment/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>50/50</td>
</tr>
<tr>
<td>200</td>
<td>100/100</td>
</tr>
<tr>
<td>300</td>
<td>150/150</td>
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<tr>
<td>400</td>
<td>200/200</td>
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<tr>
<td>500</td>
<td>250/250</td>
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<td>600</td>
<td>300/300</td>
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<tr>
<td>700</td>
<td>350/350</td>
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<td>800</td>
<td>400/400</td>
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<tr>
<td>900</td>
<td>450/450</td>
</tr>
<tr>
<td>1000</td>
<td>500/500</td>
</tr>
</tbody>
</table>

Fixed effect inverse variance-weighted model
Statistic used was odds ratio
Level of significance used to estimate power = 0.05
Power estimates used to plot the graph are saved in file called C:\Documents\temppow3.dta
Using *metapowplot*

Power curves

with 95% confidence intervals

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Sally R. Hinchliffe et al.
Stata Meeting, Stockholm 2011
Discussion

- It is hoped the suite of programs will be useful to
  1. trialists who want to assess the impact potential new trials will have on the overall evidence base.
  2. meta-analysts who want to assess the robustness of the current meta-analysis to the inclusion of future data.

- Have created prototype set of programs to allow same calculations using Bayesian approach to all meta-analyses estimation.
References

