Can I have FAITH in this Review?

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Centre for Research in Evidence Based Practice
Bond University
What do you do?

- For an acutely ill patient, you do a search
- You find several studies: some find that it works; some do not
- What do you do?
Ask somebody to find all studies, select the best, ...
Summary of the 17 studies
Summary of the 17 studies

A. Which is the smallest study?
B. Which is the largest study?
C. How many are statistically significant?
D. Which studies are “large enough”?
Summary of the 17 studies: streptokinase
How large should the study be?

In this note we will provide you with 2 “café rules” (for when you are discussing studies over an espresso), and then point to the ideas behind them and some resources for more exact calculations.

**Why is a small study a problem?**

When reading an article, we often wonder whether the study was large enough. If a study does not find a statistically significant effect (e.g., at $p<0.05$), it may be because the study was too small or because there actually is no true effect. You should check whether the confidence intervals (CIs) show that the data are consistent with the effect being clinically important, even though the effect was not “statistically significant.”

**HOW DO WE KNOW THE REQUIRED SAMPLE SIZE?**

It is helpful to have an approximate idea of the sample size requirements for different types of studies. The first approximate rule is the 50:50 rule for studies looking at dichotomous (“present or absent”) outcomes such as mortality, hospital admissions, or remissions.
What sample size is needed?

For disease X the usual mortality rate is 0%
What sample size is needed to detect a reduction in mortality?

- 100
- 1,000
- 100,000
- 1,000,000
Sample Size: Café Rule 1
The 50:50 Rule (proportions)

50 events are needed in the control group:
(For an 80% chance of finding a 50% reduction)

<table>
<thead>
<tr>
<th>Control Rate</th>
<th>Number Events</th>
<th>Control# (Rule 1)</th>
<th>Control# (Fisher exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>50</td>
<td>250</td>
<td>215</td>
</tr>
<tr>
<td>10%</td>
<td>50</td>
<td>500</td>
<td>463</td>
</tr>
<tr>
<td>5%</td>
<td>50</td>
<td>1000</td>
<td>962</td>
</tr>
</tbody>
</table>

What sample size is needed?

- There is usually a 12% mortality rate
  - You think your treatment will lower mortality by 50%
- What sample size is needed?
What sample size is needed?

- There is usually a 12% mortality rate
  - You think your treatment will lower mortality by 50%
- What sample size is needed?

- 12% means
  - 12/100 or 24/200 or 48/400
  - and 50 per 417
- Control + Treatment Groups = 834 in total
**Systematic Review or meta-analysis?**

- **A Systematic Review** is a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.

- Statistical methods (*meta-analysis*) may or may not be used to analyze and summarize the results of the included studies.
<table>
<thead>
<tr>
<th>Question</th>
<th>Step 1 (Level 1*)</th>
<th>Step 2 (Level 2*)</th>
<th>Step 3 (Level 3*)</th>
<th>Step 4 (Level 4*)</th>
<th>Step 5 (Level 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How common is the problem?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Local and current random sample surveys (or censuses)</td>
<td>Systematic review of surveys that allow matching to local circumstances**</td>
<td>Local non-random sample**</td>
<td>Case-series**</td>
<td>n/a</td>
</tr>
<tr>
<td>Is this diagnostic or monitoring test accurate? (Diagnosis)</td>
<td>Systematic review of cross sectional studies with consistently applied reference standard and blinding</td>
<td>Individual cross sectional studies with consistently applied reference standard and blinding</td>
<td>Non-consecutive studies, or studies without consistently applied reference standard**</td>
<td>Case-control studies, or &quot;poor or non-independent reference standard&quot;**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What will happen if we do not add a therapy? (Prognosis)</td>
<td>Systematic review of inception cohort studies</td>
<td>Inception cohort studies</td>
<td>Cohort study or control arm of randomized trial*</td>
<td>Case-series or case-control studies, or poor quality prognostic cohort study**</td>
<td>n/a</td>
</tr>
<tr>
<td>Does this intervention help? (Treatment Benefits)</td>
<td>Systematic review of randomized trials or n-of-1 trials</td>
<td>Randomized trial or observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
<td>Case-series, case-control studies, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
</tr>
<tr>
<td>What are the COMMON harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect</td>
<td>Individual randomized trial or (exceptionally) observational study with dramatic effect</td>
<td>Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**</td>
<td>Case-series, case-control, or historically controlled studies**</td>
<td>Mechanism-based reasoning</td>
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<tr>
<td>What are the RARE harms? (Treatment Harms)</td>
<td>Systematic review of randomized trials or n-of-1 trial</td>
<td>Randomized trial or (exceptionally) observational study with dramatic effect</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Is this (early detection) test worthwhile? (Screening)</td>
<td>Systematic review of randomized trials</td>
<td>Randomized trial</td>
<td>Non-randomized controlled cohort/follow-up study**</td>
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* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson
Is the review any good?  
**FAITH check**

- **Question** – What is the PICO?

- **Finding**  
  - Did they find most studies?

- **Appraisal**  
  - Did they

- **Include**  
  - Did they include only good ones?

- **Total up**  
  - What to they all mean?

- **Heterogeneity of PICOs, results**
Why do I need to check the review?

Most reviews do not pass minimum criteria

A study of 158 reviews*

- Only 2 met all 10 criteria
- Median was only 1 of 10 criteria met

FAITH tool = 5 criteria

* McAlister Annals of Intern Med 1999
What is the review question (PICO)?

- Population
- Intervention
- Comparison
- Outcome(s)

Using Pedometers to Increase Physical Activity and Improve Health
A Systematic Review

Dena M. Bravata, MD, MS
Crystal Smith-Spangler, MD
Vandana Sundaram, MPH
Allison L. Gienger, BA

**Context**  Without detailed evidence of their effectiveness, pedometers have recently become popular as a tool for motivating physical activity.

**Objective**  To evaluate the association of pedometer use with physical activity and health outcomes among outpatient adults.
Do pedometers increase activity and improve health?

- **Find: what is your search strategy?**
  - Databases?
  - Terms?
  - Other methods?

**METHODS**

Data Sources and Search Strategies

In collaboration with a professional librarian, we developed individualized search strategies for 7 databases: MEDLINE (January 1966 to February 2007); and EMBASE, Sport Discus, PsychINFO, Cochrane Library, Thompson Scientific (formerly known as Thompson ISI), and ERIC (January 1966 to May 2006). We used search terms such as *pedometer, activity monitor,* and *step counter.* We also reviewed the bibliographies of retrieved articles and relevant conference proceedings and contacted experts in exercise physiology for additional studies.

Do yourself then
Get neighbour’s help
FIND: Did they find all Studies?

- Check for existing systematic review?
- Good initial search
  - Terms (text and MeSH)
  - At least 2 Databases: MEDLINE, EMBASE, CINAHL, CCTR, ...
- Plus a Secondary search
  - Check references of relevant papers & reviews and
  - Find terms (words or MeSH terms) you didn’t use
  - Search again! *(snowballing)*
Is finding all published studies enough?

- Negative studies less likely to be published than ‘Positive’
- How does this happen?
- Follow-up of 737 studies at Johns Hopkins (Dickersin, *JAMA*, 1992)
  - Positive SUBMITTED more than negative (2.5 times)
## Registered vs Published Studies

**Ovarian Cancer chemotherapy: single v combined**

<table>
<thead>
<tr>
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<th>Published</th>
<th>Registered</th>
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<tbody>
<tr>
<td><strong>No. studies</strong></td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td><strong>Survival ratio</strong></td>
<td>1.16</td>
<td>1.05</td>
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<td><strong>95% CI</strong></td>
<td>1.06-1.27</td>
<td>0.98-1.12</td>
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<tr>
<td><strong>P-Value</strong></td>
<td>0.02</td>
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Simes, J. Clin Oncol, 86, p1529
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Simes, J. Clin Oncol, 86, p1529
Which are biased? Which OK?

1. All positive studies
2. All studies conducted in the Northern Hemisphere
3. All studies published in BMJ, Lancet, JAMA or NEJM
4. All studies with more than 100 patients
5. All studies registered studies
Publication Bias: Solution

- All trials registered at inception,
  - The National Clinical Trials Registry: Cancer Trials
  - National Institutes of Health Inventory of Clinical Trials and Studies
  - International Registry of Perinatal Trials

- Meta-Registry of trial Registries
  - www.controlled-trials.com
Welcome to the WHO International Clinical Trials Registry Platform

The mission of the WHO Registry Platform is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

*The registration of all interventional trials is a scientific, ethical and moral responsibility.*

What is a clinical trial?

A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

Functions
What was the “Find” date?

Of 100 systematic reviews:
Median time to a change that would effect clinical decisions was 5.5 years.

Appraise & Include studies

Did they check & select only the good quality studies?
Miscalculating NNT

Authors often miscalculate the NNT. What should we do about this?

Q1. Would the death penalty for miscalculating an NNT prevent future miscalculation? (FACT)

Q2. Should we have the death penalty for miscalculation of NNT? (VALUE)
Selective Criticism of Evidence
Biased appraisal increases polarization

Capital punishment: beliefs and contradictory studies

Lord et al, J Pers Soc Psy, 1979, p2098
Selective Criticism of Evidence

28 reviewers assessed one “study” results randomly positive or negative

<table>
<thead>
<tr>
<th></th>
<th>“Positive”</th>
<th>“Negative”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance</td>
<td>5.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Methods</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Presentation</td>
<td>4.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Summary</td>
<td>3.2</td>
<td>1.8</td>
</tr>
</tbody>
</table>

(Cog Ther Res, 1977, p161-75)
Assessment: How can you avoid biased selection of studies?

- Assessment and selection should be:
  - Standardized “Objective” OR
  - Blinded to Results

* assessment of quality blind to study outcome
Total up: pooling the results
## Meta-analysis (Forest) plot

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Treatment Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dieppe 1980&lt;sup&gt;8&lt;/sup&gt;</td>
<td>12</td>
<td>38.0 (29.0)</td>
<td>12</td>
<td>7.45</td>
</tr>
<tr>
<td>Gaffney 1995&lt;sup&gt;9&lt;/sup&gt;</td>
<td>42</td>
<td>21.7 (20.7)</td>
<td>42</td>
<td>36.26</td>
</tr>
<tr>
<td>Jones 1998&lt;sup&gt;17&lt;/sup&gt;</td>
<td>29</td>
<td>48.0 (30.0)</td>
<td>30</td>
<td>17.71</td>
</tr>
<tr>
<td>Ravaud 1999&lt;sup&gt;11&lt;/sup&gt;</td>
<td>24</td>
<td>23.7 (26.2)</td>
<td>21</td>
<td>17.36</td>
</tr>
<tr>
<td>Smith 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>38</td>
<td>20.8 (30.0)</td>
<td>33</td>
<td>21.22</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>145</strong></td>
<td><strong>20.8 (30.0)</strong></td>
<td><strong>138</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=6.87$, df=4, $P=0.14$, $I^2=41.7\%$

Test for overall effect: $z=5.01$, $P=0.00001$

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**Fig 4** Visual analogue scale for pain up to two weeks after steroid injection in knee
**Heterogeneity? Use in my patients**

Is the AVERAGE effect similar across studies?

- If NO, then WHY?
  - Study methods (RAMbo - biases)
  - PICO (Patients, Intervention, ...)

- If YES, then 2 questions
  - Effect in different individuals?
  - Which version of treatment?
Meta-analysis (Forest) plot

Are the results **similar** across studies? 3 tests

1. Eyeball” test – do they look they same?
2. Test of “Null hypothesis” of no variation (p-value)
3. Proportion of variation not due to chance ($I^2$)
Are these trials different?

<table>
<thead>
<tr>
<th>Study</th>
<th>Study group, n/N</th>
<th>Risk ratio (RR), random, with 95% confidence interval (CI)</th>
<th>Weight %</th>
<th>RR, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tankanow</td>
<td>Treatment 25/30</td>
<td>1.56 (1.08-2.26)</td>
<td>19.74</td>
<td></td>
</tr>
<tr>
<td>Arvola</td>
<td>Control 16/30</td>
<td>3.02 (1.53-5.94)</td>
<td>15.48</td>
<td></td>
</tr>
<tr>
<td>Vanderhoof</td>
<td>Treatment 13/99</td>
<td>0.54 (0.29-1.00)</td>
<td>16.42</td>
<td></td>
</tr>
<tr>
<td>Jirapinyo</td>
<td>Control 3/8</td>
<td>0.47 (0.18-1.21)</td>
<td>11.95</td>
<td></td>
</tr>
<tr>
<td>LaRosa</td>
<td>Treatment 26/60</td>
<td>0.84 (0.57-1.23)</td>
<td>19.64</td>
<td></td>
</tr>
<tr>
<td>Kotowska</td>
<td>Control 31/60</td>
<td>0.80 (0.45-1.44)</td>
<td>16.77</td>
<td></td>
</tr>
</tbody>
</table>

Total events: Treatment 115/418, Control 111/418

$\chi^2 = 23.26 (p < 0.001)$, $I^2 = 78.5\%$

$z$ score 0.02 ($p = 0.99$)
Conclusion
EBM and Systematic Review

- **EBM (quick & dirty)**
  - Steps
    1. Ask Question
    2. Search
    3. Appraise
    4. Apply
  - Time: 90 seconds
  - < 20 articles
  - This patient survives!

- **Systematic Review**
  - Steps
    1. Ask Question
    2. Search ++++ x 2
    3. Appraise x 2
    4. Synthesize
    5. Apply
  - Time: 6 months, team
  - < 2,000 articles
  - This patient is dead

Find a systematic review!! (and appraise it FAST)
Pros and cons of systematic reviews

- **Advantages**
  - Larger numbers & power
  - Robustness across PICOs
- **Disadvantages**
  - May conclude small biases are real effects
Is the review any good? FAITH check

- **Question** – What is the PICO?

- **Finding**
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- **Include**
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- **Total up**
  - What do they all mean?

- **Heterogeneity of PICOs, results**
Using review results: what do I do with my patient?

- **STUDY**: meta-analysis of behavioural interventions for insomnia adults
  - “.. confirms the efficacy of behavioral interventions for person with chronic insomnia.”

- **PROBLEM**: No regimens for ‘behavioural intervention’ described
  - Author asked: “what specific treatment regime (or regimes) would you recommend based on your review?”
  - Author response: “It was found that cognitive, behavioral and relaxation therapies all in general lead to similar improvements in sleep outcomes---although cognitive approaches might have been a bit better. The references for these studies are found in the article.”