Critical appraisal of randomised controlled trials

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3 steps to appraising an RCT

1. **Find** an RCT that addresses your clinical question

2. Assess **risk of bias** and determine if results are trustworthy

3. Determine if the **effect** is significant and generalizable
A&E clinical scenario

3 days of fever, sore throat, and headache

Neck stiffness, photophobia, confusion

Elevated CRP and white blood count

Cloudy; 30% of blood glucose; raised protein & white cell count

What is the Diagnosis? What is your next test?

Should we start this patient on steroids to improve clinical outcomes?
Clinical question? (PICO)

• 22 year old female

• Bacterial meningitis
  – 3 days of fever, sore throat, headache, neck stiffness, photophobia, confusion
  – CSF: cloudy; 30% of blood glucose; raised protein and white cell count

• Should we start steroid treatment to improve clinical outcomes?
(PICO)

• Population: In adults with acute bacterial meningitis...

• Intervention: does treatment with steroids...

• Comparison: compared to no steroids...

• Outcome: reduce the likelihood of poor outcome?

• What kind of evidence do we want?
Levels of evidence for testing effectiveness of a therapy/treatment
What is a randomized controlled trial?

• A study in which participants are randomly allocated to an experimental or comparison group

• Experimental group get an intervention

• The comparison group gets something different (no intervention, a placebo, different intervention)

• Outcomes in each group are compared to determine the effect of the intervention
What’s so special about RCTs?

Randomisation = equal groups

Steroid  No steroid

• Only difference should be the intervention

• Infer causality: can attribute differences in outcomes to the differences in the treatment
1. Find an RCT that addresses your clinical question
Corticosteroids for managing tuberculous meningitis.
Prasad K, Singh MB, Ryan H.

Streptococcus suis Meningitis: A Systematic Review and Meta-analysis.
van Samkar A, Brouwer MC, Schultsz C, van der Ende A, van de Beek D.

Adjuvant treatment with dexamethasone plus anti-C5 antibodies improves outcome of experimental pneumococcal meningitis: a randomized controlled trial.
Kasamenoitib斌 ES, Val'saner M, Morgan BP, Brouwer MC, van de Beek D.

Dexamethasone and long-term survival in bacterial meningitis.
Fritz D, Brouwer MC, van de Beek D.

Single dose oral dexamethasone versus multi-dose prednisolone in the treatment of acute exacerbations of asthma in children who attend the emergency department: study protocol for a randomized controlled trial.

The role of adjunctive dexamethasone in the treatment of bacterial meningitis: an updated systematic meta-analysis.

Investigation of the Selection and Timing of Pharmacological Therapy in Community-Acquired Bacterial Meningitis.
Sheley J, Willman D, Downen J, Bergman S.

Corticosteroids for managing tuberculous meningitis.
Prasad K, Singh MB, Ryan H.

Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis.
Ogunesi TA, Odigbo CC, Oladapo OT.

Streptococcus suis Meningitis: A Systematic Review and Meta-analysis.
van Samkar A, Brouwer MC, Schultsz C, van der Ende A, van de Beek D.

Impact of corticosteroids on experimental meningococcal sepsis in mice.
Levy M, Antonius A, Friete L, Dehmiane AE, Taha MK.

LTA4H genotype is associated with susceptibility to bacterial meningitis but is not a critical determinant of outcome.
Dunsian SJ, Tran TT, Thwaites GE, Chau TT, Phu NH, Hien TT, Farrar JJ, Wolbers M, Mai NT.

Bacterial meningitis.
Heckenberg SG, Brouwer MC, van de Beek D.

Listeria monocytogenes sequence type 6 and increased rate of unfavorable outcome in meningitis: epidemiologic cohort study.
Koopmans MM, Brouwer MC, Bijlsma MW, Rovenkamp S, Keijzers W, van der Ende A, van de Beek D.

Genetic variation in GLCCI1 and dexamethasone in bacterial meningitis.
Brouwer MC, van der Ende A, Baas F, van de Beek D.

See all (26)
Dexamethasone in Vietnamese Adolescents and Adults with Bacterial Meningitis

Nguyen Thi Hoang Mai, M.D., Tran Thi Hong Chau, M.D., Guy Thwaites, M.D., Ly Van Chuong, M.D., Dinh Xuan Sinh, M.D., Ho Dang Trung Nghia, M.D., Phung Quoc Tuan, M.D., Nguyen Duy Phong, M.D., Nguyen Hoan Phu, M.D., To Song Diep, M.D., Nguyen van Vinh Chau, M.D., Nguyen Minh Duong, M.D., James Campbell, Constance Schultsz, M.D., Chris Parry, M.D., M. Estee Torok, M.D., Nicholas White, F.R.C.P., Nguyen Tran Chinh, M.D., Tran Tinh Hien, M.D., Kasia Stepniewska, Ph.D., and Jeremy J. Farrar, F.R.C.P.

1. **Find** an RCT that addresses your clinical question

- **High proportion of Meningitis in Asia (and the study) due to *Streptococcus suis***

- **S. suis** not a common cause of meningitis in high-income countries

- Different standard of care
1. Find an RCT that addresses your clinical question

- **Population:** Age 17 years or older; suspected meningitis; cloudy CSF, bacteria on Gram staining OR leukocyte >1000 per mm³; Netherlands, Belgium, Germany, Austria, Denmark

- **Intervention:** Dexamethasone (10mg) every 6 hours for 4 days (first dose with or before antibiotics)

- **Comparison:** Placebo

- **Primary Outcome:** Glasgow outcome scale
2. Assess the **risk of bias** and decide if the results are trustworthy
Validity

• **Internal validity**: the extent to which the study is free from bias

• Bias: systematic differences between groups
  – i.e. Sicker patients in one group

• Bias can be introduced because of the design, conduct, or analysis of studies

• Low risk of bias: we can attribute differences in outcomes to the differences in the treatment given and not other variables (confounding)
Internal Validity...External Validity

• If a study is internally valid we then assess the study’s **external validity** a.k.a. **generalizability**

• **External validity**: the extent to which the results apply outside the study setting
  – Can you use the results in your situation?
  – Assess whether your patients/setting are similar enough to those in the study
Chapter 8: Assessing risk of bias in included studies

Editors: Julian PT Higgins, Douglas G Altman and Jonathan AC Sterne on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group.

Key points

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.
- An assessment of the validity of studies included in a Cochrane review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.
- Numerous tools are available for assessing methodological quality of clinical trials. We recommend against the use of scales yielding a summary score.
- The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a judgement and a support for the judgement for each entry in a 'Risk of bias' table, where each entry addresses a specific feature of the study. The judgement for each entry involves assessing the risk of bias as 'low risk', 'high risk', or 'unclear risk', with the last category indicating either lack of information or uncertainty over the potential for bias.
- Plots of 'Risk of bias' assessments can be created in RevMan.
- In clinical trials, biases can be broadly categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories.
- For parallel group trials, the features of interest in a standard 'Risk of bias' table of a Cochrane review are sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias.
- Detailed considerations for the assessment of these features are provided in this chapter.

8.1 Introduction
8.2 What is bias?
8.3 Tools for assessing quality and risk of bias
8.4 Introduction to sources of bias in clinical trials
   Table 8.4a: A common classification scheme for bias
8.5 The Cochrane Collaboration’s tool for assessing risk of bias
8.6 Presentation of assessments of risk of bias
   Figure 8.6a: Example of a ‘Risk of bias’ table
   Figure 8.6b: Example of a ‘Risk of bias graph’ Figure
   Figure 8.6c: Example of a ‘Risk of bias summary’ Figure
8.7 Summary assessments of risk of bias
   Table 8.7a: Possible approach for summary assessments
8.8 Incorporating assessments into analyses
# Chapter 8

## Table 8.4.a: A common classification scheme for bias

<table>
<thead>
<tr>
<th>Type of bias</th>
<th>Description</th>
<th>Relevant domains in the Collaboration’s ‘Risk of bias’ tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias.</td>
<td>Systematic differences between baseline characteristics of the groups that are compared.</td>
<td>• Sequence generation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Allocation concealment.</td>
</tr>
<tr>
<td>Performance bias.</td>
<td>Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.</td>
<td>• Blinding of participants and personnel.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other potential threats to validity.</td>
</tr>
<tr>
<td>Detection bias.</td>
<td>Systematic differences between groups in how outcomes are determined.</td>
<td>• Blinding of outcome assessment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other potential threats to validity.</td>
</tr>
<tr>
<td>Attrition bias.</td>
<td>Systematic differences between groups in withdrawals from a study.</td>
<td>• Incomplete outcome data</td>
</tr>
<tr>
<td>Reporting bias.</td>
<td>Systematic differences between reported and unreported findings.</td>
<td>• Selective outcome reporting (see also Chapter 10).</td>
</tr>
</tbody>
</table>
Rapid risk of bias checklist

A. Was the method of randomization truly random?
B. Was allocation adequately concealed?
C. Were groups comparable at the start?

D. Were patients and practitioners providing care blinded?
E. Was outcome assessment blinded or were outcomes objective?

F. Was there minimal loss to follow-up & losses explained?
G. Was an intention-to-treat analysis conducted?
Think about how the bias could affect the outcome

• Will it make the intervention seem more or less beneficial?

• Will it have a big impact or little impact on the effect estimates?
Selection bias

• Systematic differences between baseline characteristics of the groups

• Want comparable groups at the start

A. Random sequence generation
B. Concealed allocation
A. Generation of an unpredictable allocation sequence
B. Adequate allocation concealment

- Patients and investigators enrolling patients shouldn’t know which group the next patient is going to; can’t know the sequence.

- Biased if participant’s decision to provide consent or a recruiter’s decision to enrol a participant is influenced by knowledge of which group a patient would be in if they participated.
B. Adequate allocation concealment

**Best**
Central telephone/computer

**Doubtful**
Things that can be tampered with (numbered, opaque, sealed envelopes)
Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study

Allocation concealment and estimates of intervention effects

We included 102 meta-analyses in our analysis of associations between allocation concealment and estimates of intervention effects (fig 1). Of the 804 trials in these meta-analyses, 272 (34%) had adequate allocation concealment. Overall, intervention effect estimates were exaggerated by 17% in the trials with inadequate or unclear allocation concealment compared with those with adequate allocation concealment.
## Allocation concealment impacts results

<table>
<thead>
<tr>
<th>Comparison (No of meta-analyses)</th>
<th>No of trials*</th>
<th>Ratio of odds ratios</th>
<th>Ratio of odds ratios (95% CI)</th>
<th>P value of test of interaction</th>
<th>Variability in bias† (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (102)</td>
<td>532 v 272</td>
<td></td>
<td>0.83 (0.74 to 0.93)</td>
<td>–</td>
<td>0.11 (&lt;0.001)</td>
</tr>
</tbody>
</table>

* Inadequately or unclearly concealed vs adequately concealed
† Between-meta-analysis heterogeneity variance
**Treatment**

Patients were randomly assigned to receive dexamethasone sodium phosphate (Oradexon), at a dose of 10 mg given every six hours.

Dexamethasone, n=157  
OR  
Placebo, n=144
A. Method of randomisation?
B. Adequate allocation concealment?
C. Were groups comparable at the start?

Balanced treatment assignments within each hospital were achieved with the use of a computer-generated list of random numbers in blocks of six. The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up. Treatment assignments were concealed from all investigators, but in an emergency, investigators had access to the sealed, opaque envelopes containing the assignments; two emergencies occurred. Patients were
Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>DEXAMETHASONE GROUP (N=157)</th>
<th>PLACEBO GROUP (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>44±18</td>
<td>46±20</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>89 (57)</td>
<td>80 (56)</td>
</tr>
<tr>
<td>Basis for eligibility — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteria in CSF on Gram’s staining</td>
<td>116 (74)</td>
<td>99 (69)</td>
</tr>
<tr>
<td>No bacteria in CSF on Gram’s staining but CSF white-cell count &gt;1000 per mm³</td>
<td>38 (24)</td>
<td>42 (29)</td>
</tr>
<tr>
<td>Cloudy CSF only</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Duration of symptoms before admission — hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Range</td>
<td>1–336</td>
<td>1–167</td>
</tr>
<tr>
<td>Seizures — no. (%)</td>
<td>15 (10)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Findings on admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF pressure — cm of water†</td>
<td>37±13</td>
<td>34±14</td>
</tr>
<tr>
<td>Score on Glasgow Coma Scale‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Range</td>
<td>3–14</td>
<td>3–14</td>
</tr>
<tr>
<td>Score &lt;8, indicating coma — no. (%)</td>
<td>25 (16)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>Papilledema — no. (%)§</td>
<td>6 (7)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Cranial-nerve palsy — no. (%)</td>
<td>14 (9)</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Hemiparesis — no. (%)</td>
<td>10 (6)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>CSF culture — no. (%)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>58 (37)</td>
<td>50 (35)</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>50 (32)</td>
<td>47 (33)</td>
</tr>
<tr>
<td>Other bacteria</td>
<td>12 (8)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Negative bacterial culture</td>
<td>35 (23)</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Indexes of CSF inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White-cell count — per mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>8185±12,541</td>
<td>7438±10,688</td>
</tr>
<tr>
<td>Median</td>
<td>3667</td>
<td>3498</td>
</tr>
<tr>
<td>Range</td>
<td>7–123,000</td>
<td>3–76,000</td>
</tr>
<tr>
<td>Protein — g/liter</td>
<td>4.3±3.0</td>
<td>4.7±3.2</td>
</tr>
<tr>
<td>Glucose — mg/dl∥</td>
<td>27±31</td>
<td>27±29</td>
</tr>
<tr>
<td>Positive blood culture — no. (%)**</td>
<td>72 (53)</td>
<td>60 (47)</td>
</tr>
</tbody>
</table>
Balanced treatment assignments within each hospital were achieved with the use of a computer-generated list of random numbers in blocks of six. The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up. Treatment assignments were concealed from all investigators, but in an emergency, the principal investigator could alter the assignment.
Block randomisation attempts to ensure equal group sizes.
Performance bias

• Systematic differences in how patients are treated and in how patients behave during a study (other than the intervention)

• Goal is equal treatment/behaviour other than the intervention

D. Were patients and practitioners providing care blinded?
Blinding impacts the results

Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study

Blinding and estimates of intervention effects

Figure 2 shows the associations between blinding and estimates of intervention effects, based on 76 meta-analyses containing 746 trials, of which 432 (58%) were blinded. Overall, estimates of intervention effects were exaggerated by 7% in non-blinded compared with blinded trials (ratio of odds ratios 0.93 (0.83 to 0.94).
D. Were patients and practitioners providing care blinded?

**Methods** We conducted a prospective, randomized, double-blind, multicenter trial of adjuvant treatment with dexamethasone, as compared with placebo, in intravenously for four days, or placebo that was identical in appearance to the active drug. The study medication was given 15 to 20 bers in blocks of six. The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up. Treatment
Performance bias

- Other differences in treatment?

...appearance to the active drug. The study medication was given 15 to 20 minutes before the parenteral administration of antibiotics. After the interim analysis, the protocol was amended to allow administration of the study medication with the antibiotics.
Detection bias

• Systematic differences in how outcomes are determined?

• Goal: outcomes assessed the same way for both groups

E. Was outcome assessment blinded or were outcomes objective
   – Objective: cannot be influenced by investigators’ judgment
   – Death, preterm birth, etc.
Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study
<table>
<thead>
<tr>
<th>Comparison (No of meta-analyses)</th>
<th>No of trials*</th>
<th>Ratio of odds ratios</th>
<th>Ratio of odds ratios (95% CI)</th>
<th>P value of test of interaction</th>
<th>Variability in bias† (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality (18)</td>
<td>79 v 121</td>
<td></td>
<td>1.04 (0.95 to 1.14)</td>
<td>0.011</td>
<td>0.01 (0.27)</td>
</tr>
<tr>
<td>Other outcomes (58)</td>
<td>235 v 311</td>
<td></td>
<td>0.83 (0.70 to 0.98)</td>
<td>0.18</td>
<td>0.18 (0.001)</td>
</tr>
<tr>
<td>Objective outcomes (44)</td>
<td>210 v 227</td>
<td></td>
<td>1.01 (0.92 to 1.10)</td>
<td>0.01</td>
<td>0.08 (0.001)</td>
</tr>
<tr>
<td>Subjective outcomes (32)</td>
<td>104 v 205</td>
<td></td>
<td>0.75 (0.61 to 0.82)</td>
<td></td>
<td>0.14 (0.001)</td>
</tr>
</tbody>
</table>

* Non-blinded v blinded
† Between-meta-analysis heterogeneity variance
• Were outcome assessments blinded?

bers in blocks of six. The code was not broken until the last patient to be enrolled had completed eight weeks of follow-up. Treatment
Other outcome considerations

- Relevant for patients?
- Valid and reliable?
- Sample size calculation: was the study “powered” to detect a difference?
Outcomes

• Primary outcome
  – Glasgow Outcome Score 1 - 4 eight weeks after randomisation (unfavourable outcome)
  – 1: death, 2: vegetative state, 3: severe disability, 4: moderate disability

• Secondary outcomes
  – Death
  – Focal neurological abnormalities
  – Hearing loss (audiologic examination)
  – GI bleed
  – Fungal infection
  – Herpes zoster
  – Hyperglycaemia
outcome as a score of 1 to 4. The Glasgow Outcome Scale has frequently been used in trials involving stroke and other brain injuries. It is a well-validated scale with good interobserver agreement.\textsuperscript{13,14} Several groups have used it to assess the functional and clinical...
Sample size calculation

Was there a sample size calculation?

Did the study include enough participants?

Calculation of the required sample size was based on the assumption that dexamethasone would reduce the proportion of patients with an unfavorable outcome from 40 to 25 percent. With a two-sided test, an alpha level of 0.05, and a power of 80 percent, the analysis required 150 patients per group. The analysis of outcomes
301 Patients enrolled

157 Patients received dexamethasone as assigned

144 Patients received placebo as assigned
Attrition bias

• Systematic differences in withdrawals from the study

F. Was there minimal loss to follow-up & losses explained?

G. Was an intention-to-treat analysis conducted?

• Goal: groups should be equal at the end of the study
F. Minimal loss to follow-up and losses explained

• “5-and-20 rule of thumb” for follow-up
  – <5% little bias
  – 5 to 20% small bias
  – >20% poses serious threats to validity
G. Intention-to-treat analysis

- Once a patient is randomised, he/she is analysed in their assigned group

- Regardless of status: lost to follow-up, never received treatment, or crossed over

- Benefit: groups stay equal, maintain power, estimate of “real world” effectiveness

- Missing data
  - Last observation carried forward
  - Multiple imputation
F. Was there minimal loss to follow-up and were the reasons explained?

G. Did they do an ITT analysis?
301 Patients enrolled

157 Patients received dexamethasone as assigned

11 Patients withdrawn early from treatment
Did not meet inclusion criteria (3)
Adverse event (4)
Other (4)

3 Patients lost to follow-up
11 Patients died
143 Patients followed for 8 wk

9% drop out

144 Patients received placebo as assigned

11 Patients withdrawn early from treatment
Did not meet inclusion criteria (1)
Adverse event (1)
Other (9)

4 Patients lost to follow-up
21 Patients died
119 Patients followed for 8 wk

10% drop out

157 Patients included in analysis at 8 wk
(last observation carried forward)

144 Patients included in analysis at 8 wk
(last observation carried forward)

ITT?
Risk of bias done!

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated randomisation list, block size 6</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was concealed</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>The study was double-blind</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No loss to follow-up</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Inclusion chart provided. Intention-to-treat analysis</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No indication of other bias</td>
</tr>
</tbody>
</table>
3. Determine if the effect is significant and generalizable
What was the effect on the primary outcome?

Plain English, no stats

GOS 1-4 “unfavorable outcome”
1: death
2: vegetative state
3: severe disability
4: moderate disability
Is the effect statistically significant?

- **P values**
  - Probability that what you are observing is due to chance
  - $<0.05$ is statistically significant

- **Confidence intervals**
  - Range of values that likely include the real value
  - Repeat study 100 times, value would be in that range 95% of the time
  - Narrower the range, the more reliable
  - Statistically significant if range does not include 1 for a ratio or 0 for a difference
Different ways to describe the effect

Relative measures use division (ratio of risk)

- $0.15/0.25 = 0.59$ (Relative risk)
- $0.59 - 1 = 0.41$ (Expressed as a relative risk reduction)
- Dexamethasone group had a 41% reduction in the risk of unfavorable outcome compared to the placebo group

Absolute measures use subtraction (difference in risk)

- $0.15 – 0.25 = 0.10$ (Absolute risk reduction or risk difference)
- **Number Needed to Treat** to avoid ONE unfavourable outcome
- $1/$risk difference = **NNT** (better description for clinical significance)
- $1/0.10 = 10$ (treat 10 patients to avoid ONE unfavourable outcome)
Described the effect, assessed significance

What else do we want to know to make a decision?
### Table 5. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Dexamethasone Group (N=157)</th>
<th>Placebo Group (N=144)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2 (1)</td>
<td>5 (3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Blood transfusion required</td>
<td>2 (1)</td>
<td>4 (3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Stomach perforation</td>
<td>1 (1)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>50 (32)</td>
<td>37 (26)</td>
<td>0.24</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>6 (4)</td>
<td>4 (3)</td>
<td>0.75</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>8 (5)</td>
<td>4 (3)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
**Generalizable effect that helps us decide on treatment?**

- External validity: were the patients and setting in the study similar to ours?

- Consider patient characteristics, feasibility and features of the intervention, clinical setting and standards of routine care
  - Really selected patient populations
  - High vs. low income countries
  - Complex interventions

- European countries, adults, similar clinical presentation, likely similar standards of care
• 22 year old female
• Bacterial meningitis
  – 3 days of fever, sore throat, headache, neck stiffness, photophobia, confusion
  – CSF: cloudy; 30% of blood glucose; raised protein and white cell count
• Should we use steroid treatment to improve clinical outcomes?
Resources

• Cochrane
  • http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm

• Centre for Evidence-Based Medicine
  • http://www.cebm.net/year-4-medical-students/
Questions?

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