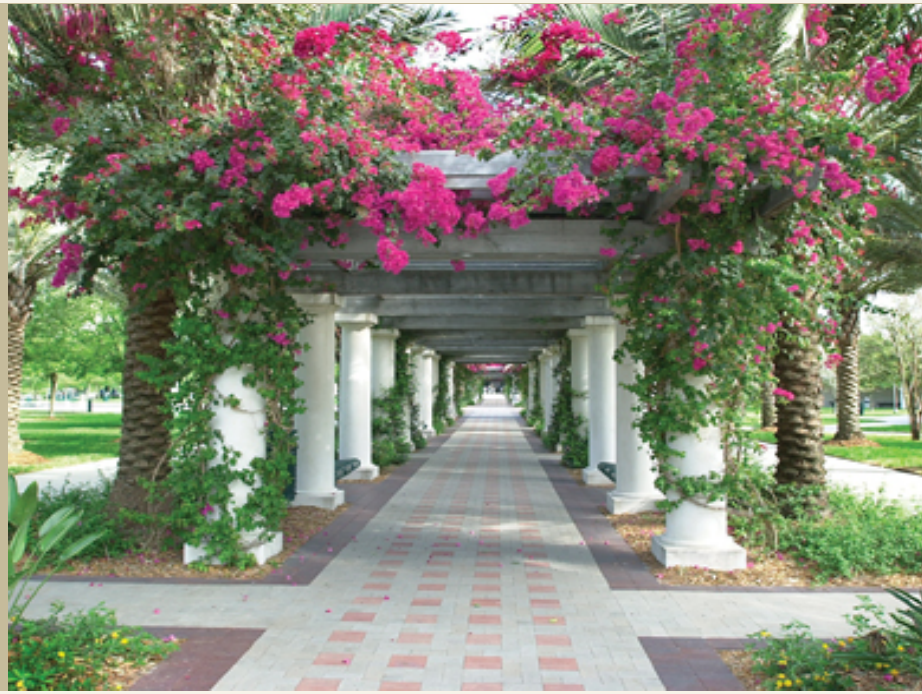
Critical appraisal of a randomized controlled trial



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Overview

- Background
- Steps for critical appraisal
- Discussion
- Hands on exercise

Background

Whenever a trial is conducted there are 3 possible explanations for the results:

- findings are correct (truth),
- represents random variation (chance), and
- they are influenced by systematic error (bias).

Random error is deviation from the “truth” and happens due to play of chance (e.g. trials with small sample, etc.).

Courtesy: Dr. Djulbegovic

Background

- Systematic distortion of the estimated intervention effect away from the “truth” can also be caused by inadequacies in the design, conduct, or analysis of a trial.
- Several studies have shown that bias can obscure up to 60% of the real effect of a health care intervention.
- A mounting body of empirical evidence shows that "biased results from poorly designed and reported trials can mislead decision making in health care at all levels”.

Courtesy: Dr. Djulbegovic

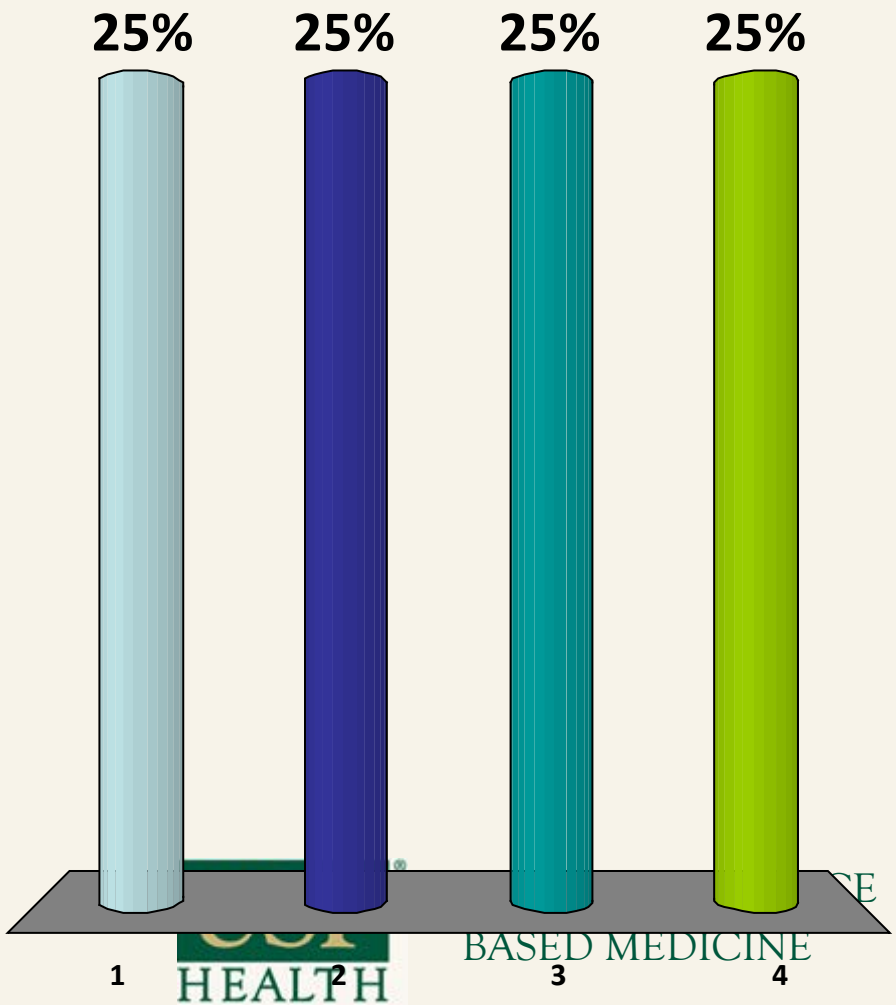
Risk of Bias

- Generation of randomization sequence
- Allocation concealment
- Description of drop outs
- Intention to treat analysis
- Blinding

- Randomization

Why do we need randomization?

1. To create equal groups
2. To have improved external validity
3. To reduce selection bias
4. All of the above



Was the assignment of patients to treatments randomised?

- *Centralised computer randomisation* is ideal and often used in multi-centred trials.
- Smaller trials may use an *independent* person (e.g. the hospital pharmacy) to “police” the randomization.

- Where to find **:** Methods section

Baseline Characteristics
are they similar?

YOU

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Were the groups similar at the start of the trial?

- If the randomisation process worked (that is, achieved comparable groups) the groups should be similar. The more similar the groups the better it is.
- There should be some indication of whether differences between groups are statistically significant (i.e. p values).

- Where to find: *Results* should have a table of "Baseline Characteristics"

Aside from the allocated treatment, were groups treated equally?

- Apart from the intervention the patients in the different groups should be treated the same, e.g., additional treatments or tests.

- Where to find: Look in the *Methods* section for the follow-up schedule, and permitted additional treatments, etc and in *Results* for actual use.

Description of drop outs

- Losses to follow-up should be minimal – preferably less than 20%.
- Reasons for drop outs / loss to follow up should be reported.
- However, if few patients have the outcome of interest, then even small losses to follow-up can bias the results.

- <u>Where to find:</u> Results. You will need to read the results section to clarify the number and reason for losses to follow-up.

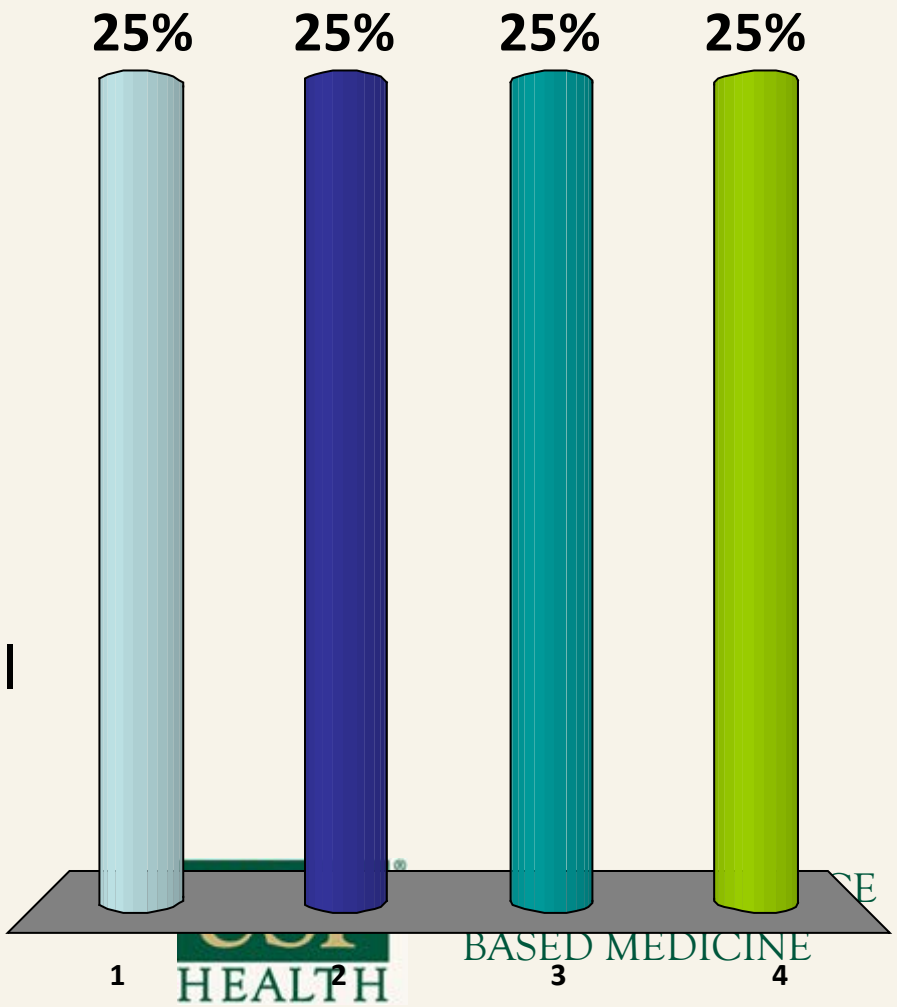
Intention to treat analysis

versus

Per protocol analysis

What is the ideal way to analyze data for treatment related harms

1. Use all randomized patients
2. Consider all patients who have received treatment
3. Consider patients who have experienced at least one adverse events
4. Consider patients who have experienced grade III / IV adverse events



Intention to treat analysis (ITT)

- ITT: Number randomized = number analyzed
- Per protocol: Number analyzed = Number receiving the Rx

- Benefits data : ITT
- Harms data: Per protocol analysis

- Where to find: *Results* section should say how many patients were randomised (eg., Baseline Characteristics table) and how many patients were actually included in the analysis.

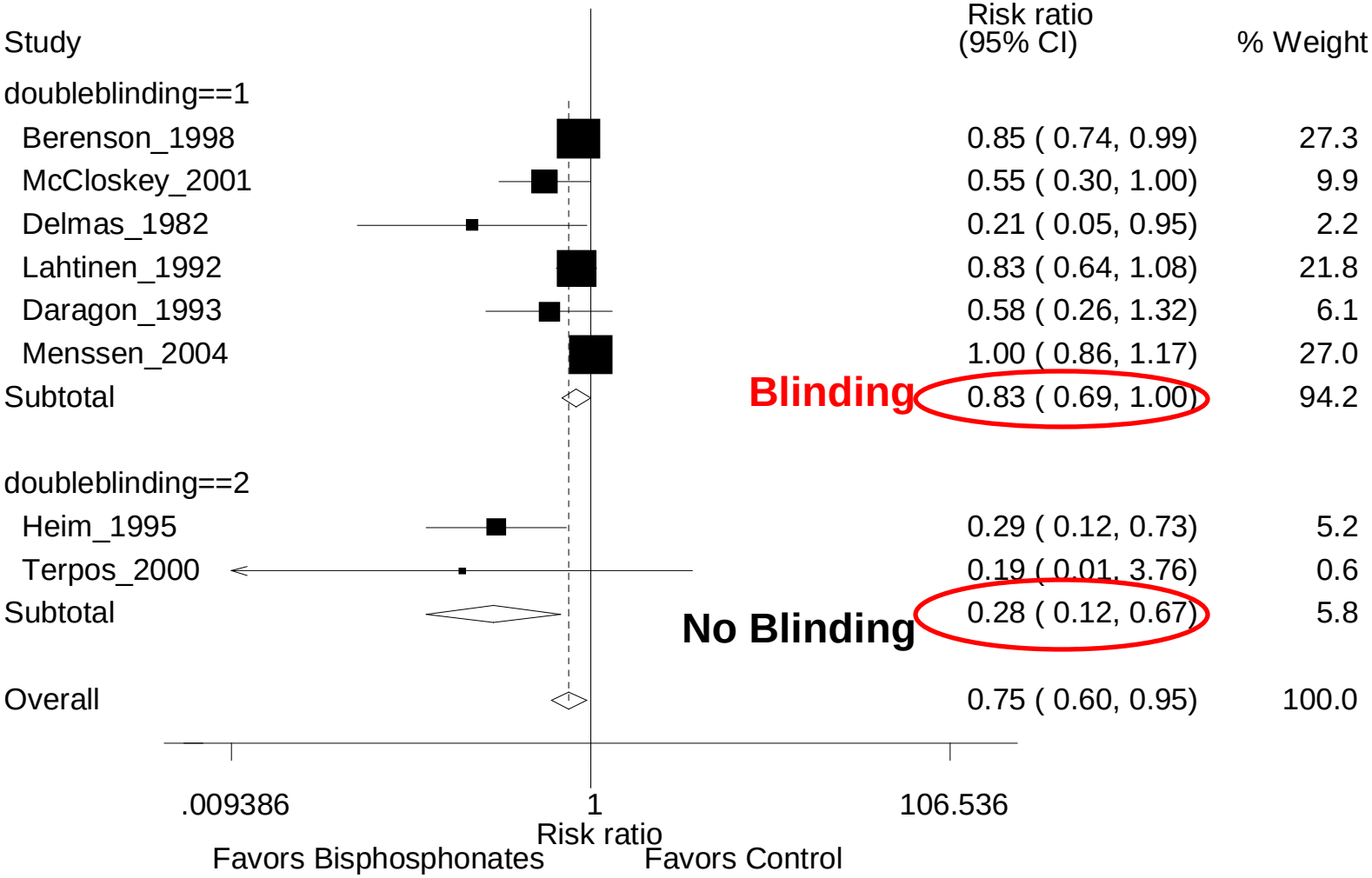
If the study mentions that it is “double blind” it is considered good quality reporting.

33%	1. Yes
33%	2. No
33%	3. May be

Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?

- It is ideal if the study is 'blinded'.
- If the outcome is *objective* (eg., death) then blinding is less critical.
- If the outcome is *subjective* (eg., symptoms or function) then blinding of the outcome assessor is critical.
- Where to find: First, look in the *Methods* section to see if there is some mention of masking of treatments, eg., placebos with the same appearance or sham therapy. Second, the *Methods* section should describe how the outcome was assessed and whether the assessor/s were aware of the patients' treatment.

Blinding matters !



Risk of random error

- Whether the alpha, beta errors, and sample size calculations are reported?
- Is the sample size calculation conducted considering the “primary outcome” of the study?

- Where to find: Methods / statistical methods

What is missing?

- In the intensive pathway, we aimed to recruit 1080 patients (540 per group) to test the hypothesis that open laparoscopy for gallstone removal was not inferior to laparoscopic removal of gallstones, with a hazard ratio of 1.2 and 80% power at a 5% significance level.

sample size

beta

alpha

What is the outcome of interest?

How precise was the estimate of the treatment effect?

- The true risk of the outcome in the population is not known and the best we can do is estimate the true risk based on the sample of patients in the trial. This estimate is called the point estimate.
- We can gauge how close this estimate is to the true value by looking at the confidence intervals (CI) for each estimate.

- If the confidence interval is fairly narrow then we can be confident that our point estimate is a precise reflection of the population value.
- If the value corresponding to no effect falls outside the 95% confidence interval then the result is statistically significant at the 0.05 level.

Will the results help me in caring for my patient? (External Validity/Applicability)

The questions that you should ask before you decide to apply the results of the study to your patient are:

- Is my patient so different to those in the study that the results cannot apply?
- Is the treatment feasible in my setting?
- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?

Thank you.

Any questions?

Case1

- 107 children, age 1 month to 22 years who presented to an ED who had experienced at least three episodes of vomiting in the previous 24 hours thought to be secondary to an acute gastroenteritis and required intravenous fluids.
- Patients were excluded if they had received any antiemetic therapy within 72 hours of enrolment, had a history of hepatic disease or had diarrhea lasting more than 7 days.
- Ondansetron 0.15 mg/kg IV was given as a single dose.

Key results

- 38 (70%) of the 54 patients in the group who received ondansetron and 27 (51%) in the group that received placebo had complete cessation of vomiting ($p = 0.04$)
- Fourteen patients (26%) who received ondansetron and 16 patients (30%) who received placebo were hospitalized ($p>0.05$)

Some observations

- No alpha / beta error reported with the original sample size and the outcome for which it was calculated.
- The study was supported by a grant from Glaxo Wellcome Inc. who manufacture ondansetron No testing was done to determine the cause of gastroenteritis.
- In a subgroup analysis excluding patients who had serum CO2 <14 mEq/l or had previously received intravenous hydration, 3 of 43 (7.5%) patients who received ondansetron and 11 of 47 (23%) who received placebo required hospitalization (p = 0.04)

Bottomline

- There is currently insufficient evidence to justify the use of oral or intravenous ondansetron in children suffering from acute viral gastroenteritis.
- A large, well constructed prospective study is needed to answer this question.