

0:1 verloren und trotzdem gewonnen

Non-Inferiority Trials erklärt

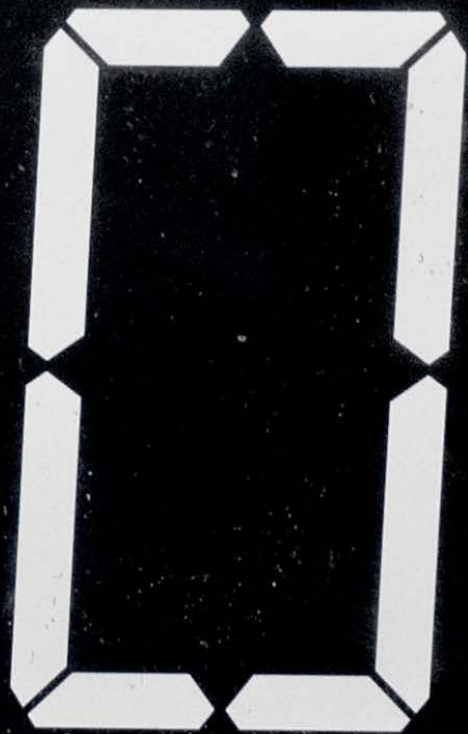
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CTU Lecture, 11.12.2018

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The advantage of "0"

No difference/tie

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<http://berbisdorfer-sv.de>

The advantage of "0"

Result $\neq 0 \rightarrow$ difference



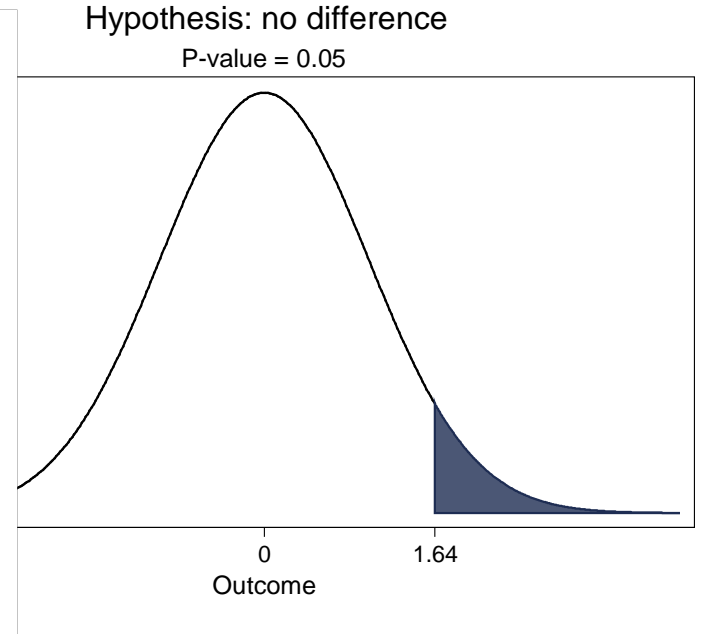
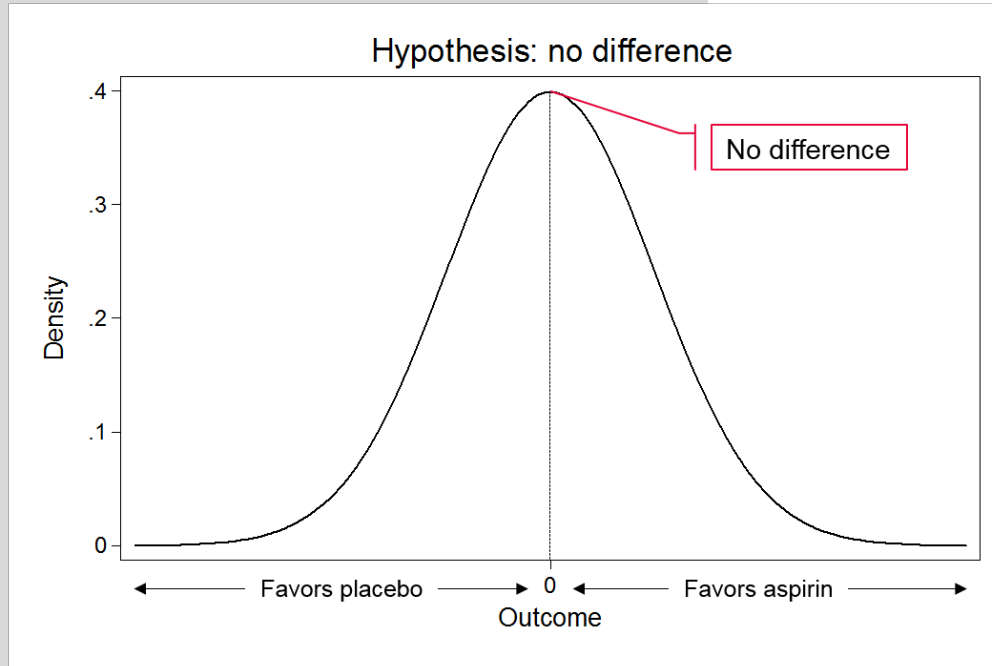
Superiority trials

The usual approach (framework)



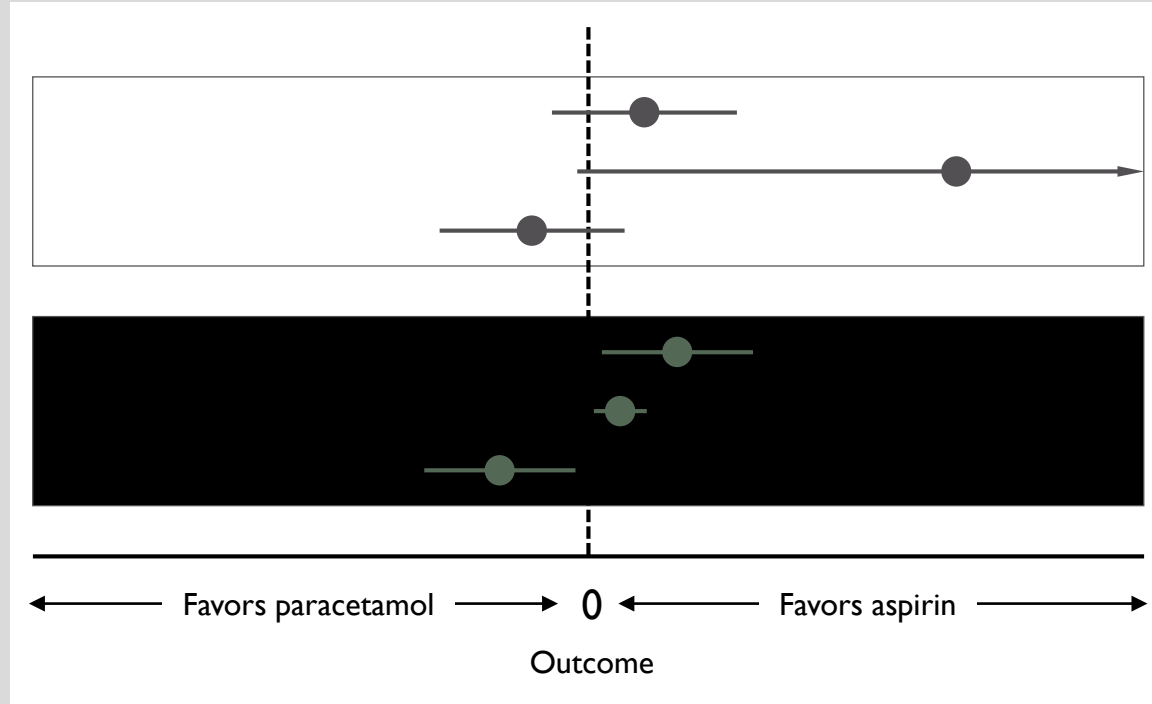
Usual null-hypothesis test

Difference == 0 (or > 0)



Observed difference

95% confidence interval



See CTU Lecture June 2018

Possibility for confusion

Sidenote

- Test for equality
- Test for non-inferiority
- Test for superiority
 - Clinical versus statistical superiority
- Test for equivalence

Issues in non-inferiority trials

Selection of topics

- Defining control and experimental
 - Assay sensitivity
 - Choosing between superiority and non-inferiority
- Determining the non-inferiority margin
- Which estimand (earlier days: intention-to-treat versus per-protocol)?
- Switching frameworks

Selecting the control intervention

Issues

- Assay sensitivity
 - Ability to distinguish an effective from an ineffective (less effective) treatment e.g. is the control better than placebo/no intervention/historical control (also in the non-inferiority trial)
 - Establish by historical evidence
 - Related to indirect evidence/comparisons (→ network meta-analysis)
 - Or establish by three arm trial design e.g. placebo
- Defining the standard of care (not different to superiority trials?)

Which one is the standard (control)?

Example: perioperative ventilation (PROMISE-02)

- Ventilation with 80% fraction of inspired oxygen ($FiO_2=0.8$) in unselected patients undergoing general anesthesia reduces risk of surgical site infections
 - WHO guidelines recommends $FiO_2=0.8$ (regardless of oxygen saturation)
- Routine practice in patients at risk for coronary heart disease is to maintain oxygen saturation of 94-98% ($FiO_2=0.3$) i.e. ventilate to target
- Research question: what are the cardiovascular (adverse) effects

Which one is the standard (control)?

Example: perioperative ventilation (PROMISE-02)

- Standard: $\text{FiO}_2=0.8$, Experimental: ventilate to target
 - Non-inferiority regarding surgical site infections
 - Superiority regarding cardiovascular (adverse) effects
- Standard: ventilate to target, Experimental: $\text{FiO}_2=0.8$
 - Non-inferiority regarding cardiovascular (adverse) effects
 - (Superiority regarding surgical site infections)

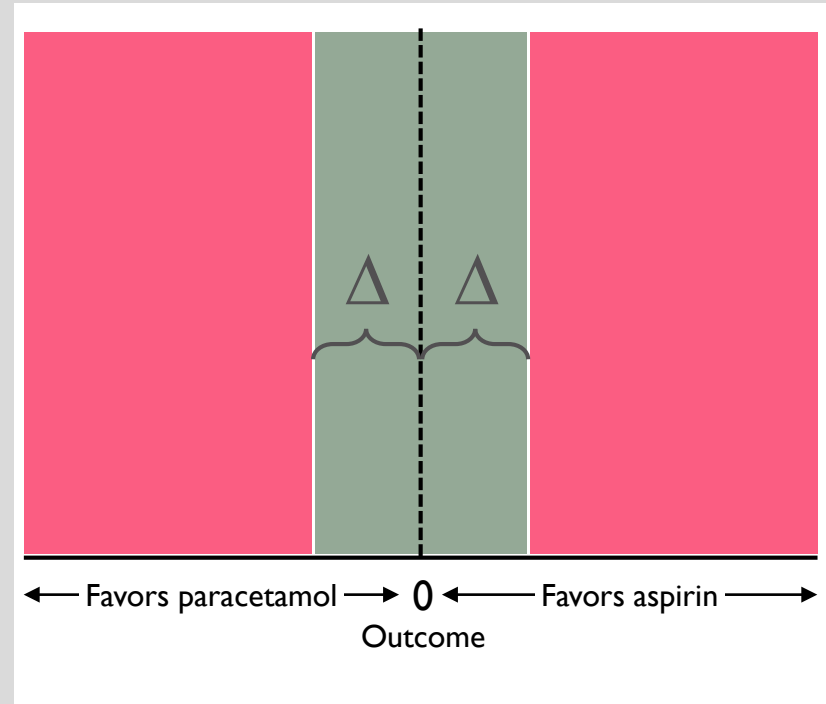
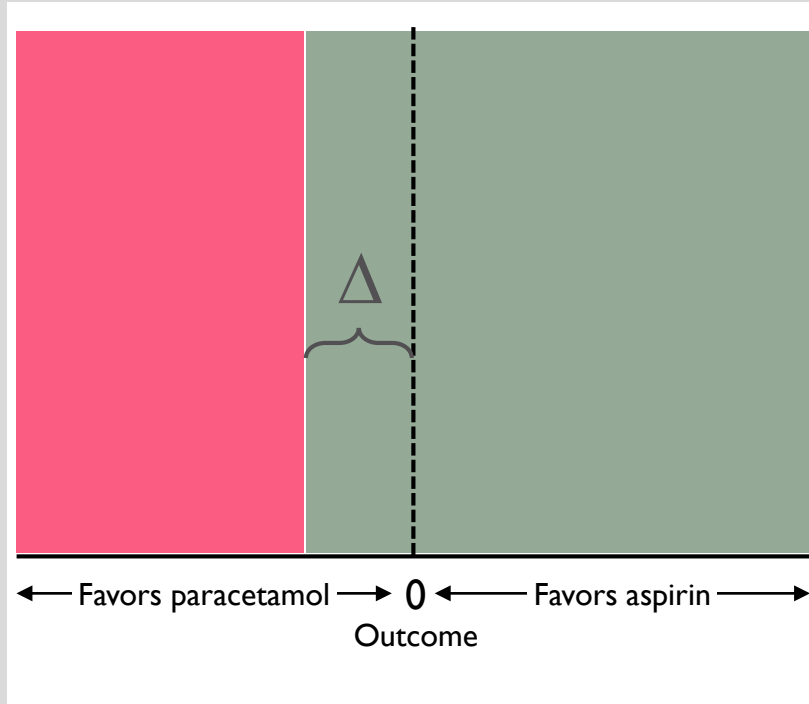
Which one is the standard (control)?

Example: anticoagulation start (ELAN)

- Patients with non-valvular atrial fibrillation and stroke
- Anticoagulation start based on
 - transformation of stroke and bleeding risk score
 - 1-3-6-12 rule
 - >2 weeks
- No evidence but 'only' clinical practice
- Research question: when to start (early versus late)?

The non-inferiority margin

Not worse by ...



The non-inferiority margin

Determination

- Clinical judgement, patient perspective
 - Delphi approach
 - Ad-hoc
- Synthesis (point-estimate) approach
 - Does the margin ensure that the experimental treatment is better than placebo/no intervention (or historical control)?
 - Or: does it preserve a certain fraction e.g. 50% of the effect?

The non-inferiority margin

Issues

- Context specific
- Subjective/arbitrary
- May change over time
- Only lower bound of CI or also point estimate?

The non-inferiority margin

Example:robotic cystectomy

In patients with bladder cancer, robotic cystectomy was non-inferior to open cystectomy for 2-year progression-free survival ($p_{\text{non-inferiority}}=0.001$).

The non-inferiority margin

Example: robotic cystectomy

*... non-inferiority would be established if the lower bound of the one-sided 97.5% CI for the treatment difference... was greater than **-15** percentage points [difference in 2-year progression-free survival]*

Which estimand?

Analysis population

- Widespread misconception: main analysis using per-protocol set only
- Intention-to-treat and per-protocol analysis need to agree
- No naïve per-protocol analysis
 - Confounding
 - Causal modelling techniques

Switching frameworks

Interpretation of results

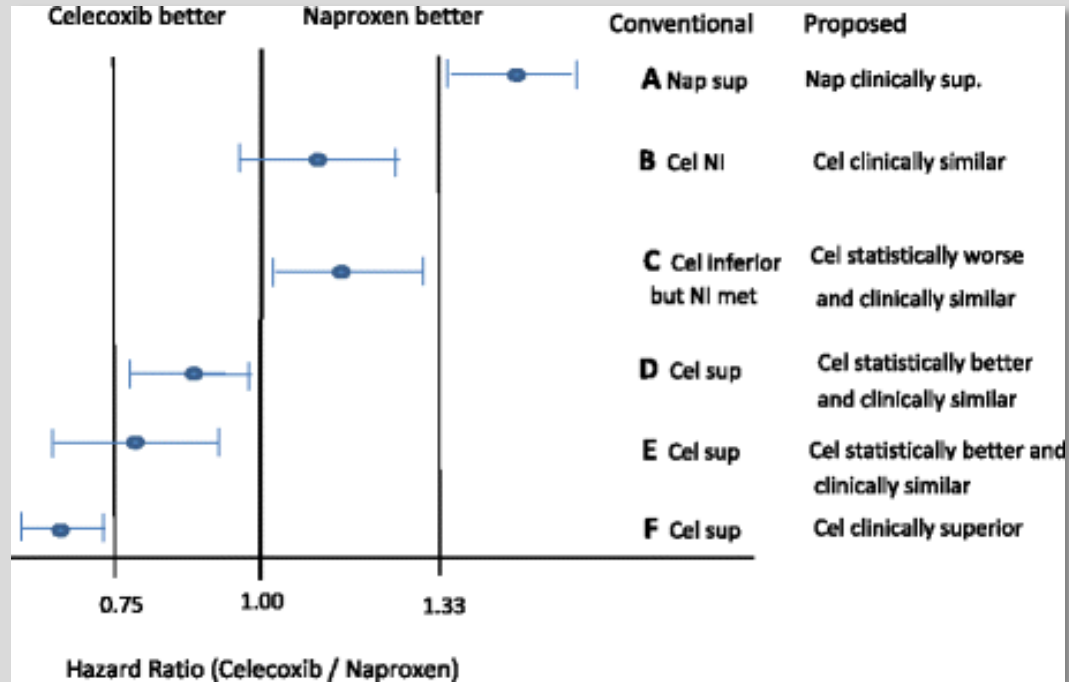


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- Clinical versus statistical significance/superiority

Switching frameworks

Interpretation of results



Switching frameworks

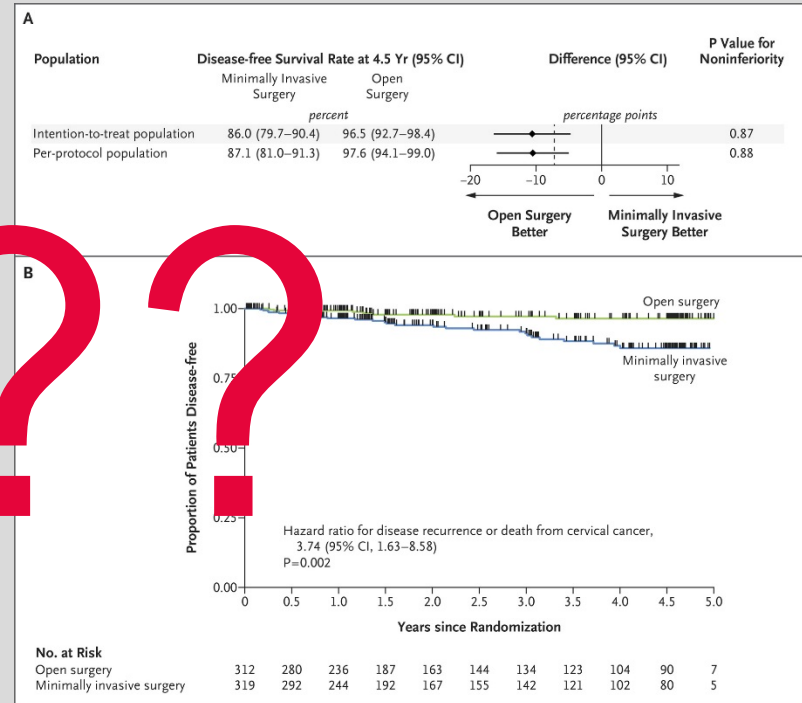
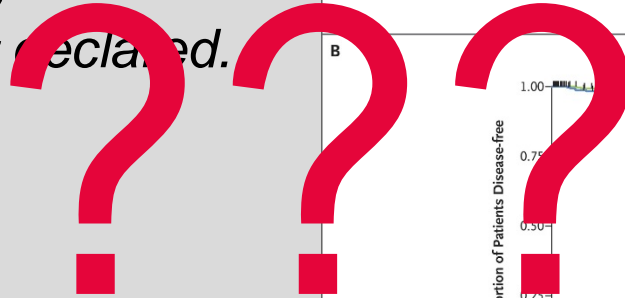
Non-inferiority \leftrightarrow superiority

- The strict null hypothesis testing framework sets strict boundaries
- No problem
 - Switching to superiority after non-inferiority was shown
- (Very) Difficult
 - Switching to non-inferiority after superiority could not be shown

Switching frameworks

Non-inferiority ↔ superiority

The lower boundary of the confidence interval included the noninferiority margin of -7.2 percentage points, so noninferiority was not declared.



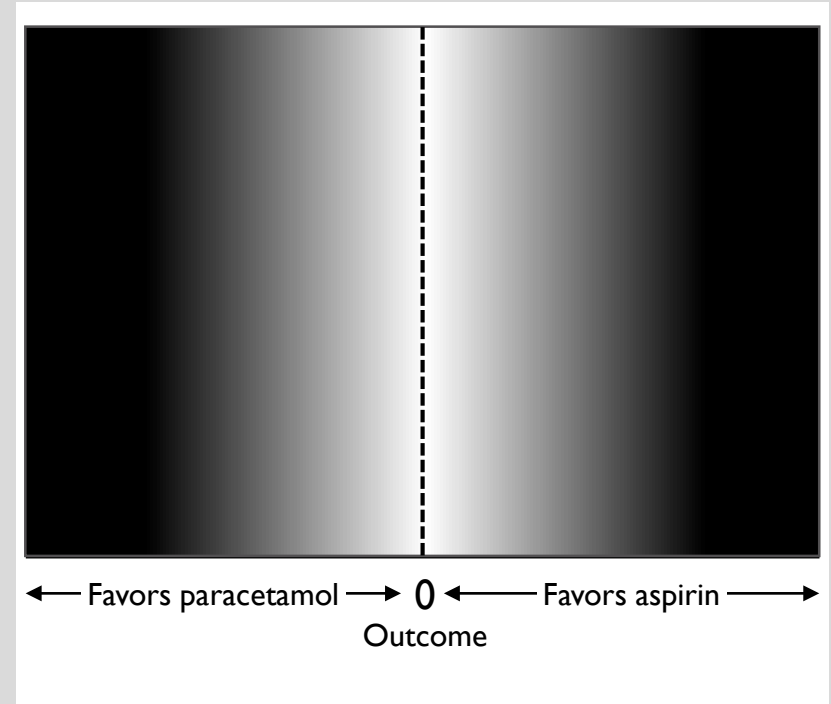
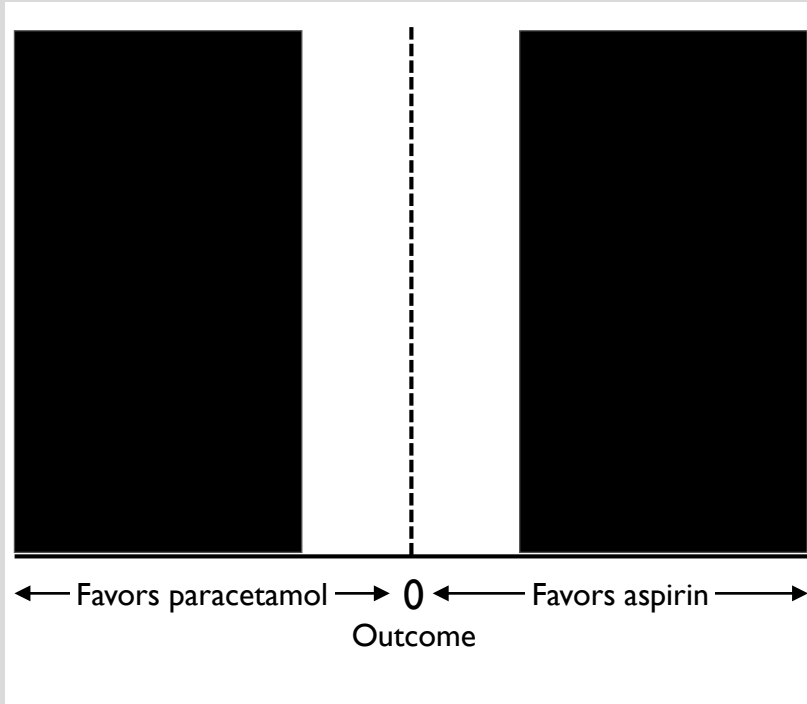
Other issues

Final remarks

- Non-inferiority implies two research questions:
 1. Non-inferior in one (some) aspect(s)
 2. Superior in other aspect(s)
- Dichotomia

Our world

Black and white or grey?



See CTU Lecture June 2018

Thank you for your attention!

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References

- Dhayat NA 2018: BMC Nephrology; 19:349
- Dunn DT 2018: Trials; 19:499.
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- Parekh DJ 2018: Lancet 391:2525–36.
- Ramirez PT 2018: N Engl J Med 379:1895-904.
- Trials 2011; 12:106.

Photos

- pixabay

