



# How to Read a Clinical Trial

# Objectives

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- Be able to define validity as it relates to a clinical trial.
- Be able to determine clinical utility and efficacy of a clinical trial.

# Key Terms

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- Validity
- Clinical utility
- Surrogate marker
- Number needed to treat (NNT)

# Three Questions

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- Validity
  - ▣ Sound design.
  - ▣ Reproducible results.
- Efficacy
  - ▣ Effective results.
- Clinical utility
  - ▣ Usefulness in practice.

# Validity

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## □ 6 Questions:

1. How were patients selected for the study?
  - ▣ Think about the potential for bias (volunteer effect, etc.).
2. Were patients randomly assigned to treatment groups?
  - ▣ Random assignment to treatment groups avoids procedure selection bias.

# Validity

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4. Were all patients who entered the study accounted for at its conclusion?
  - ▣ E.g. In a study comparing surgical and medical therapy for bilateral carotid artery stenosis, 167 patients were entered into a randomized clinical trial. The results were reported for those 151 patients who survived the initial hospitalization without any adverse outcome. The surgical group had a 27% reduction in the risk of future TIAs, CVAs, or death ( $p=0.02$ ). However, the 16 missing patients were excluded due to CVA or death during the initial hospitalization. 15 of these 16 patients were in the surgical treatment group. When these patients were included, the results were no longer statistically significant.

# Validity

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4. Were patients analyzed in the groups to which they were initially assigned?
  - ▣ Intent-to-treat analysis
  - ▣ Preserves integrity of the randomization process.
5. Were the investigators and the patients blind as to the assignments to treatment groups?
6. Were the groups treated similarly in all respects other than the experimental intervention?

# Efficacy

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- How large was the treatment effect?
  - ▣ This may be presented as a relative risk or a relative risk reduction.
- How precise is the estimate?
  - ▣ 95% confidence intervals are now commonly used, but
  - ▣ P-values may also be useful.
- Was a surrogate marker used?
  - ▣ Is it a true predictor of disease or just a co-variable?
  - ▣ What are the sensitivity and specificity of the marker?



# Clinical Utility

- Were all clinically relevant outcomes reported?
  - Trial of a monoclonal antibody (HA-1A) for the treatment of gram negative sepsis (NEJM, mid-1990s).
    - 543 patients were enrolled, and only 200 patients were subsequently found to have gram negative bacteremia. In those 200 patients, HA-1A significantly improved mortality. However, in the 543 patients as a whole there was no difference in mortality between the treatment and placebo groups.
    - The FDA found that in the 343 patients without gram negative bacteremia HA-1A was associated with increased mortality. This was not reported in the original paper.

# Clinical Utility

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- Were the study participants similar to your patients?
- Is the treatment feasible in your practice?
- Are the benefits worth the potential harms or cost of the new therapy?
- Number Needed to Treat (NNT)
  - True measure of clinical utility - allows a risk benefit analysis.
  - Calculated:  $1 / \text{absolute risk reduction}$ .

# Clinical Utility

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- E.g. In treatment group, 2% have the event you are trying to prevent (eg MI), and 4% of placebo groups have it.
  - ▣ The relative risk is  $2/4 = .5$  or a 50% reduction – looks great!!
  - But the absolute reduction is only 2%.
  - ▣ The NNT is  $1/.02 = 50$  needed to treat to prevent one event.
    - This number then can be used to develop a risk benefit assessment.

# Summary

- Does the study have a sound design?
  - ▣ Representative, non-biased sampling.
  - ▣ Valid analysis of patient groups.
- How large was the treatment effect?
- Is the study clinically useful?
  - ▣ All clinically-relevant outcomes reported.
  - ▣ Benefits outweigh risks or potential costs.

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