

EBM-TBL
Session #5
10-7-13
Therapy
Results and Applicability

This week's EBM learning will focus on:

- Recapping the basic statistical concepts used to analyze results of therapy studies
- Statistical significance versus clinical significance
- Understanding NNT treatment thresholds
- The clinical utility of confidence intervals

Please also see the pdf attachment.

Statistical significance (at the 5% level) refers to the probability that the outcome of one treatment arm is identical to the other treatment arm. By convention, if the probability is less than or equal to 5%, we conclude that they are in fact different. This is the famous $p \leq 0.05$.

When using confidence intervals, the interpretation depends on how the result (the treatment effect) was calculated. If the ARR confidence interval does not include the point of equivalence of the two treatment arms, we conclude that the two treatments are different (there is less than a 5% chance that they are identical).

As an example;

ARR = 15% [- 23%, 19%]

The ARR is calculated from CER-EER. When CER=EER (i.e., the outcomes of the two treatments are identical), this is the point of equivalence and equals 0. When the confidence interval includes the point of equivalence (0 in this case), then the two treatments are not statistically different from one another. Put another way, when the confidence interval crosses 0, the results are not statistically significant.

RR = 2.4 [0.6, 3.6]

The relative risk (RR) is calculated from EER/CER. When CER=EER, this is the point of equivalence and in this case equals 1. When the confidence interval crosses 1, the results are not statistically significant. Note: we will not be using RR in this session.

Clinical significance is the amount of difference between the new treatment and the control which would have clinical meaning. In the context of a therapy study, clinical meaning refers

to crossing a treatment threshold, i.e., the amount of difference or level at which one would start treatment.

How does one determine the clinical significance? One weighs the benefits and the risks of the new treatment, the severity of the disease, and the risks of not treating (risks may include costs as well) and determines the minimum treatment effect that would be clinically meaningful.

This is easier said than done.

For example, the considerations for treating otitis media with a new antibiotic are far different than treating non-Hodgkins lymphoma with a new chemotherapeutic agent – though in both cases, considerations focus on benefits and risks of the new medication, and the risks (or benefits) of non-treatment or treatment with the old medication. In any case, explicitly or subconsciously - correctly or incorrectly reasoned - a decision to use a new treatment includes a minimally acceptable level of clinical significance.

As an example: a study determines that the ARR of a new antibiotic (compared to amoxicillin) to treat otitis media is 3% and is statistically significant. The NNT for this ARR is 33. If one's NNT treatment threshold is no more than 10, one would not use this antibiotic. Even though it was found to be statistically significant from control, it is not clinically significant.

On the other hand, one may chose an NNT treatment threshold much higher than 10, given the dangerous nature of non-Hodgkins lymphoma.

Finally, in the context of the NNT, we will consider the clinical utility of the 95% confidence interval.

To explain, we will use an example. Following weighing the various risks and benefits of a new medication for migraine headaches, one generates a *clinically* significant (meaningful) NNT of 20. If 20 is the largest number of patients you would be willing to treat to benefit one patient and you want to be confident (95% confident) that the NNT of new treatment is less, look at the **upper level** of the confidence interval.

The new treatment is statistically different from control and its NNT is 10 with a 95% confidence interval of [6, 13]. Since the confidence interval does not cross 20, the new treatment is clinically significant. If the confidence interval were [3, 24], it would cross 20 and therefore one could not be 95% confident that one would not have to treat more than 20 patients.

Please see the pdf document that follows for a brief verbal and graphical summary of many of the above concepts.

EBM: Therapy

EXAMPLE

Illustrating analysis of results, especially absolute risk reduction (ARR), number needed to treat (NNT), and 95% confidence intervals

THERAPY

- 13 year old
- 1 year history of migraines
- Affecting school
- Limited relief with acute medications
- Her parents ask about using **Topiramate**

Answerable Clinical Question

- P: In patients with chronic migraine headaches,
- I: what is the therapeutic efficacy of topiramate,
- C: compared to placebo,
- O: in cutting in half the headache frequency?

- What follows are the results from a study evaluating the therapeutic benefit of Topiramate compared to placebo (it was a randomized, double blind, intention to treat study – i.e., valid)

Analyzing the Results

The **Results** placed in a

2X2 Table

	< 50% Reduction in headaches	≥ 50% Reduction in headaches	Total
Placebo (Control)	88	26	114
Topiramate (100mg) (Experimental)	61	59	120

Analyzing the Results

	< 50% Reduction in headaches	≥ 50% Reduction in headaches	Total
Placebo (Control)	88	26	114
Topiramate (100mg) (Experimental)	61	59	120

CER = Control Event Rate = $88/114 = 0.77 = 77\%$

EER = Experimental Event Rate = $61/120 = 0.51 = 51\%$

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Absolute Risk Reduction =

$$\begin{aligned} \mathbf{ARR} &= \mathbf{CER} - \mathbf{EER} \\ &= \mathbf{0.77} - \mathbf{0.51} = \mathbf{0.26} \\ &= \mathbf{77\%} - \mathbf{51\%} = \mathbf{26\%} \end{aligned}$$

Analyzing the Results

	< 50% Reduction in headaches	≥ 50% Reduction in headaches	Total
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CER = Control Event Rate = $88/114 = 0.77 = 77\%$

EER = Experimental Event Rate = $61/120 = 0.51 = 51\%$

Absolute Risk Reduction = $ARR = CER - EER = 0.77 - 0.51 = 0.26$ (26%)

Number Needed to Treat

$$\mathbf{= NNT = 1/ARR = 1/0.26 = 4}$$

95% Confidence Interval

- 95% Confidence Interval (CI)
 - If the study were repeated 100 times, 95 out of 100 times the result would be found within the 95% CI
 - You can be 95% confident that the “true” result is found within the 95% CI
- The bigger the sample, the “tighter” the 95% CI
- ARR = 26% [15%, 38%] *Statistically significant*
- NNT = 4 [3, 7]

$$\text{NNT} = 1/\text{ARR} = 1/0.26 = 4$$

Applicability – Treatment Threshold

- Are you confident “enough” that you will not have to treat more patients than your personal NNT (= treatment threshold) to see the benefit in one patient?
- Do you want to be **95% confident** that the actual number of patients you will have to treat to see the benefit in one patient is no more than your personal cutoff?
- *Look at the upper end of the 95% CI*

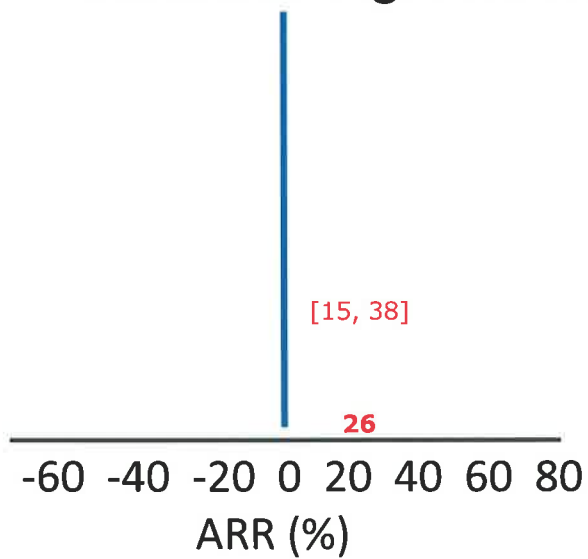
Applicability

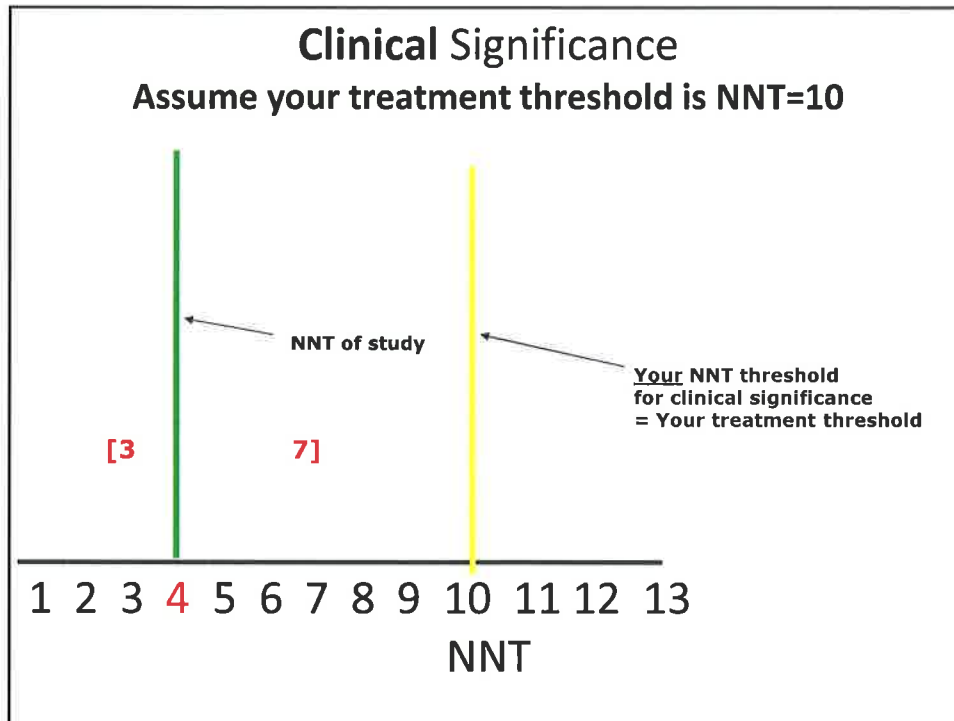
- ARR = 26% [15%, 38%]
- NNT = 4 [3, 7]

Example: “How many patients would you be willing to treat in order for one patient to benefit from 100 mg/d topiramate (50% reduction in headache frequency)?”

- If you want to be **95% confident** that the actual number of patients you will have to treat to see the benefit in one patient is no more than your personal cutoff...
 - **Look at the upper end of the 95% CI**

Statistical Significance





- ### Clinical Significance
- Assume your treatment threshold is $NNT=10$
- “If you’re willing to treat 10, you’re willing to treat 7”
 - i.e., you are 95% confident that the actual number of patients you will have to treat is no more than your personal treatment threshold
 - Therefore, the results are both statistically and clinically significant