EBM-TBL
Session #4

Analyzing the Results of a Therapeutic Trial

Please focus on calculating ARR (from CER and EER) and NNT and understanding 95% confidence intervals.
Do not focus on RRR, RR, and p-value.

measured wherever possible. Often, outcomes are expressed as mean values of measures rather than numbers of individuals having a particular outcome. The use of means can hide important information about the characteristics of patients who have improved and, perhaps more importantly, those who have got worse.

Are the results important?

Two things you need to consider are how large is the treatment effect and how precise is the finding from the trial.

In any clinical therapeutic study there are three explanations for the observed effect:

1. Bias.
2. Chance variation between the two groups.
3. The effect of the treatment.

Once bias has been excluded (by asking if the study is valid), we must consider the possibility that the results are a chance effect.

p Values

Alongside the results, the paper should report a measure of the likelihood that this result could have occurred if the treatment was no better than the control. The *p* value is a commonly used measure of this probability.

For example, a p value of <0.01 means that there is a less than 1 in 100 (1%) probability of the result occurring by chance; $p<0.05$ means this is less than 1 in 20 probability.

Quantifying the risk of benefit and harm

Once chance and bias have been ruled out, we must examine the difference in event rates between the control and experimental groups to see if there is a significant difference. These **event rates** can be calculated as shown below:

	Control	Experimental	
Event	a	b	Control event rate (CER) = a / (a+c)
No event	c	d	Experimental event rate (EER) = b / (b+d)

Relative risk reduction (RRR)

Relative risk reduction is the percentage reduction in events in the treated group event rate (EER) compared to the control group event rate (CER):

$$RRR = \frac{CER - EER}{CER}$$

Absolute risk reduction (ARR)

Absolute risk reduction is the absolute difference between the control and experimental group.

$$ARR = CER - EER$$

ARR is a more clinically relevant measure to use than RRR. This is because RRR "factors out" the baseline risk, so that small differences in risk can seem significant when compared to a small baseline risk. Consider the two sets of sample figures below, where the same RRR is found even though the treatment shows ten times greater absolute benefit in sample 1:

	CER	EER	ARR	RRR
1	0.36 (36%)	0.34 (34%)	0.36 – 0.34 = 0.02 (2%)	(0.36 – 0.34) / 0.36 = 5.6%
2	0.036% (3.6%)	0.034 (3.4%)	0.036 – 0.034 = 0.002 (0.2%)	(0.036 – 0.034) / 0.036 = 5.6%

Number needed to treat (NNT)

Number needed to treat is the most useful measure of benefit, as it tells you the absolute number of patients who need to be treated to prevent one bad outcome. It is the inverse of the ARR:

$$NNT = \frac{1}{ARR}$$

Mortality in patients surviving acute myocardial infarction for at least 3 days with left ventricular ejection fraction < 40% (ISIS-4, *Lancet* 1995)		Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
Placebo: control event rate (CER)	Captopril: experimental event rate (EER)	$\frac{CER - EER}{CER}$	CER – EER	**1 / ARR**
275 / 1116 = 0.2464 (24.64%)	228 / 1115 = 0.2045 (20.45%)	$\frac{0.2464 - 0.2045}{0.2464}$ = 17%	0.2464 – 0.2054 = 0.0419 (4.19%)	**1 / 0.0419 = 24** (NNTs always round UP)

Confidence intervals (CIs)

Any study can only examine a sample of a population. Hence, we would expect the sample to be different from the population. This is known as *sampling error.* Confidence intervals (CIs) are used to represent sampling error. A 95% CI specifies that there is a 95% chance that the population's "true" value lies between the two limits. The 95% CI on an NNT = 1 / the 95% CI on its ARR:

$$\text{95\% CI on the ARR} = \pm 1.96 \times \sqrt{\frac{CER \times (1 - CER)}{\#\text{ of control patients}} + \frac{EER \times (1 - EER)}{\#\text{ of exper. patients}}}$$

If a confidence interval crosses the "line of no difference" (i.e. the point at which a benefit becomes a harm), then we can conclude that the results are *not statistically significant.*

Relative risk (RR)

Relative risk is also used to quantify the difference in risk between control and experimental groups. Relative risk is a ratio of the risk in the experimental group to the risk in the control group.

$$RR = EER / CER$$

Thus, an RR below 1 shows that there is less risk of the event in the experimental group. As with the RRR, relative risk does not tell you anything about the baseline risk, or therefore the absolute benefit to be gained.

Summary

An evidence-based approach to deciding whether a treatment is effective for your patient involves the following steps:

1. Frame the clinical question.
2. Search for evidence concerning the efficacy of the therapy.
3. Assess the methods used to carry out the trial of the therapy.
4. Determine the NNT of the therapy.
5. Decide whether the NNT can apply to your patient, and estimate a particularised NNT.
6. Incorporate your patient's values and preferences into deciding on a course of action.

Further reading

Bandolier Guide to Bias: http://www.jr2.ox.ac.uk/bandolier/band80/b80-2.html

Dawes M *et al. Evidence-Based Practice: a primer for health care professionals.* Edinburgh: Churchill Livingstone, 1999, pp. 49–58.

Greenhalgh P. *How to Read a Paper, 2nd ed.* London: BMJ Books, 2001.

Guyatt GH *et al.* Users' Guides to the Medical Literature II: How to use an article about therapy or prevention A: Are the results of the study valid? *JAMA* 1993;**270**(21):2598–601.

Guyatt GH *et al.* Users' Guides to the Medical Literature II: How to use an article about therapy or prevention B: What were the results and will they help me in caring for my patients? *JAMA* 1994:**271**(1):59–63.

ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995:**345**:669–85. See also the CAT at www.eboncall.co.uk

Sackett DL *et al. Evidence-Based Medicine: How to practice and teach EBM.* New York: Churchill Livingstone, 2000.

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

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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%

Analyzing the Results

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Placebo (Control)	88	26	114
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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

= 77% - 51% = 26%

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%

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

Number Needed to Treat

= NNT = 1/ARR = 1/0.26 = 4

Analyzing the Results

- 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%]
- NNT = 4 [3, 7]

Statistically significant?

NNT = 1/ARR = 1/0.26 = 4

- NOTE: YOU DO NOT NEED TO CALCULATE CI'S. THERE ARE WEB-BASED CALCULATORS THAT CAN DO IT FOR YOU