

# Risky Business: Understanding Risk and the Application of Number- Needed-to-Treat

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# Session Objectives

- By the end of this session, participants will be able to:
  1. Define, compare and contrast the concepts of: absolute risk reduction (or increase), relative risk reduction (RRR), number-needed-to-treat (NNT) and number-needed-to-harm (NNH)
  2. Discuss how NNT and NNH provide tools to translate the outcomes of large clinical studies to individual patient situations
  3. Calculate NNT and NNH from raw data, OR/RRR, and study outcomes; identify published NNT resources and be able to implement these concepts in a typical first year physician assistant curriculum

# What's the Problem?

- *You hear the claims....*

# How do Randomized Controlled Trial (RCT) and Systematic Review (SR) data apply to the Individual Patient?

- The risk of the individual may not be similar to the “average risk” of the group(s) studied
- Examination of subgroups in a study is limited due to a smaller sample; therefore invalid conclusions may be drawn
- Effective treatments or preventive measures may not always translate to benefit in a given individual

# How do Study Results Apply to Our Clinical Patient?

- A more clinically useful measure than the OR and RR is the number of patients that would need to be treated with the proposed agent (drug, intervention, surgery, etc.) in order to result in 1 additional benefit or 1 additional harm
  - Number needed to treat (NNT)
  - Number needed to harm (NNH)

# Absolute Risk Reduction

- *Absolute risk reduction (ARR)* is the **difference** in risk between *treatment* (experimental) and *control* groups

# Relative Risk Reduction

- *Relative risk reduction (RRR)* is the **ratio** of the absolute risk reduction (ARR) divided by the control event rate (CER)

# Absolute versus Relative Risk Reduction

- Hypothetical Example:
  - 100 women take a new drug to see if it reduces the incidence of breast cancer (experimental) vs. 100 women who take a placebo (control). After 5 years of follow-up, 2 women in the treatment group get breast cancer, compared to 4 in the control group.
    - 100 women in **treatment group** followed 5 years → 2 develop breast cancer
    - 100 women in **control group** followed 5 years → 4 develop breast cancer



# Absolute Risk Reduction

- **Absolute risk reduction** (ARR) is CER (control event rate) – EER (experimental event rate)

$$\text{ARR} = \text{CER} - \text{EER}$$

- CER 4/100(4%) – 2/100(2%) = ARR of 2% fewer cases of breast cancer

# Relative Risk Reduction

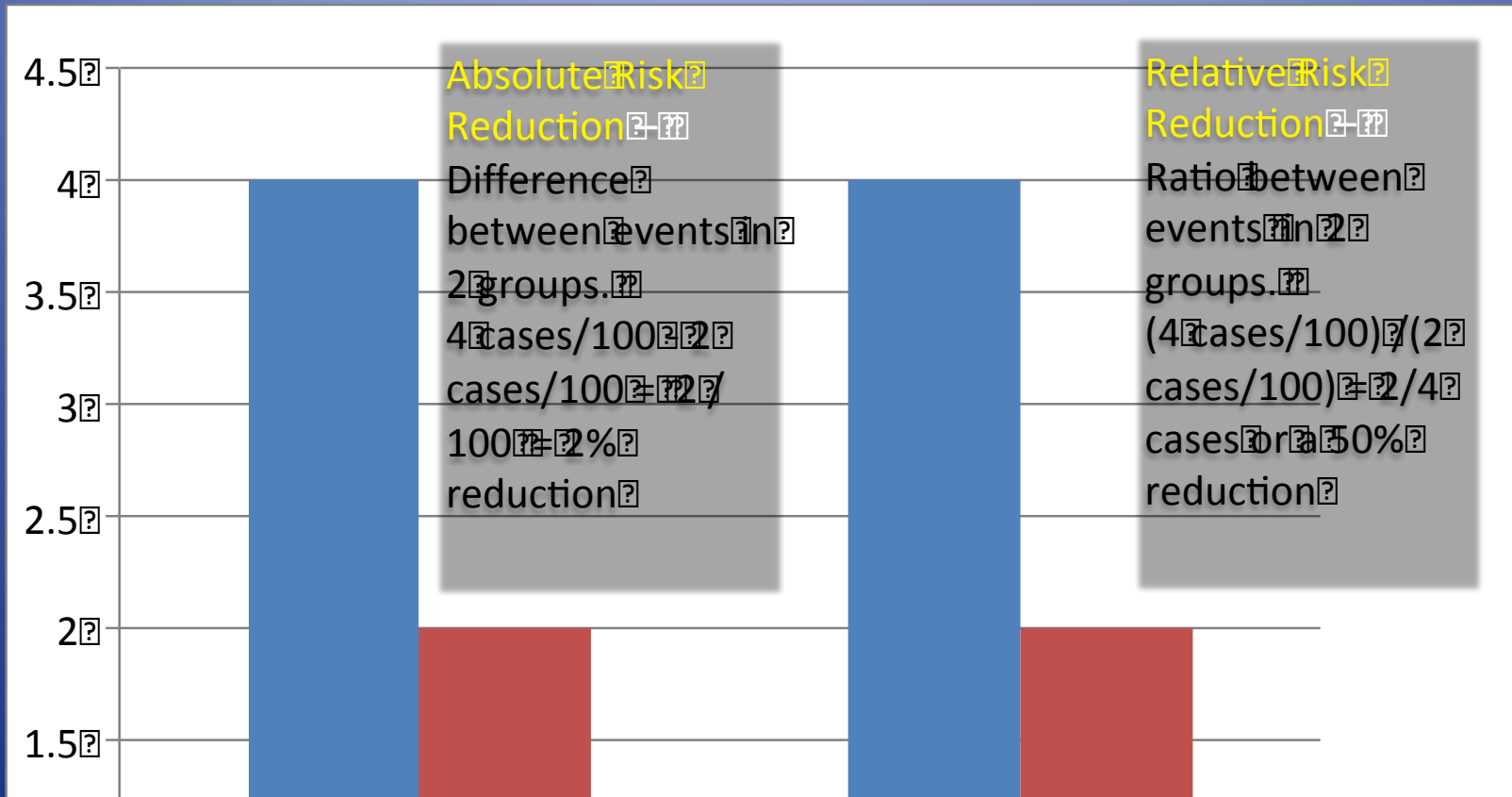
- *Relative risk reduction (RRR)* for this example is:

$$\frac{(\text{CER} - \text{EER})}{\text{CER}}$$

- $\text{RRR} = \frac{4 - 2}{4} = 50\% \text{ RRR}$  (here you are comparing the reduction of breast cancer cases in the treatment to that of the control group, rather than to everyone in the study at risk for disease)

*So RRR can look more favorable than ARR even though it is measuring risk from the same study...*

# Absolute vs. Relative Risk Reduction



# Clinically Useful Measures of the Effects of Treatment

- Need to consider:
  - Event rate – need to determine both control event rate (CER) vs. experimental event rate (EER)
- Absolute Risk Reduction (ARR)
  - $ARR = CER - EER$
- Number Needed to Treat (NNT)
  - $NNT = \frac{1}{ARR}$  (or can use  $100/ARR$  when ARR is a %)

# Caveats for Applying NNTs

- Keep in mind there needs to be a specified dimension of follow up time – “How long do you have to treat to prevent the bad outcome or obtain the good outcome?”
- NNT is an estimate and should be viewed in the context of confidence intervals, especially for small studies
- The closer to “1” the better because it means every patient benefits from treatment

# Number Needed to Treat (NNT)

- **NNT = 1/ARR**
  - The ARR is the amount by which your therapy reduces the risk of the bad outcome
- For example, if your drug reduces the risk of a bad outcome from 50% to 30%, the ARR is:

$$\text{ARR} = \text{CER} - \text{EER}$$

- $\text{ARR} = 0.5 - 0.3 = 0.2$  (20%)
- So.... $\text{NNT} = 1/\text{ARR} = 1/0.2 = 5^*$
- \*Interpretation: 5 people need to be treated to prevent 1 bad outcome

# Number Needed to Harm (NNH)

- $NNH = 1/ARI$  (absolute risk increase)
- $ARI = EER$  (intervention/treatment harm rate) –  $CER$  (control harm rate)
- The ARI is the amount by which your therapy increases the risk of the bad outcome
- So for example, if your drug increases the risk of a bad outcome to 40% from 10%
- $ARI = 0.4 - 0.1 = 0.3$  (30%)
- $NNH = 1/ARI = 1/0.3 = 3$
- Interpretation: 3 people need to be treated for 1 bad outcome (harm) to occur

## Example: NNT– giving thrombolytic therapy for an acute MI to prevent death

- $NNT = 1/ARR$
- If thrombolytic therapy given to acute MI patients reduces the death rate from 12% in the control group to 9% in the treatment group, the absolute risk reduction (ARR) is  
 $12\% (0.12) - 9\% (0.09) = 3\% (0.03)$
- So the number needed to treat (NNT) is  $1/0.03$  or 33
- Interpretation: in the setting of an acute MI, one would need to treat 33 patients with thrombolytic therapy to save one life



Example : NNH – giving thrombolytic therapy for an acute MI to prevent death but evaluating the risk of a hemorrhagic stroke

- $NNH = 1/ARI$
- When giving thrombolytic therapy for acute MI to prevent death, there is an absolute risk increase for an intracranial hemorrhage of 1% (0.01), so the number needed to harm (NNH) is  $1/0.01$  or 100
- 100 patients would needed to be given thrombolytic therapy to cause one fatal intracranial hemorrhage
- These calculations aren't the final word in terms of the relative values of benefit and harm - it is important to balance the benefits of an intervention with the potential harms and incorporate both in the decision making process

So what is the discussion you  
have with your patient?

# NNT & NNH Conversions

- Equations to convert Relative Risk Reduction (RRR) and Relative Risk Increase (RRI) to our individual patient
- $NNT = 1/(PEER \times RRR)$
- $NNH = 1/(PEER \times RRI)$

\*PEER = patient expected event rate -often substitute control event rate (CER)

# Table for Common NNTs and NNHs

Deriving NNTs from a treatment's Odds Ratio and the observed or expected Event Rates of untreated groups or individuals:

CER or PEER	Odds Ratios																		
	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9		1.5	2	2.5	3	3.5	4	4.5	5	10
	NNTs for efficacy										NNHs for harm								
<b>0.05</b>	41	46	52	59	69	83	104	139	209		43	22	15	12	9	8	7	6	3
<b>0.1</b>	21	24	27	31	36	43	54	73	110		23	12	9	7	6	5	4	4	2
<b>0.2</b>	11	13	14	17	20	24	30	40	61		14	8	5	4	4	3	3	3	2
<b>0.3</b>	8	9	10	12	14	18	22	30	46		11	6	5	4	3	3	3	3	2
<b>0.4</b>	7	8	9	10	12	15	19	26	40		10	6	4	4	3	3	3	3	2
<b>0.5</b>	6	7	8	9	11	14	18	25	38		10	6	5	4	4	3	3	3	2
<b>0.7</b>	6	7	9	10	13	16	20	28	44		13	8	7	6	5	5	5	5	4
<b>0.9</b>	12	15	18	22	27	34	46	64	101		32	21	17	16	14	14	13	13	11

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# Terminology Definitions and Equations

Test characteristic	Definition
Absolute Risk Reduction (ARR)	<p>Absolute risk reduction (ARR) is the amount by which therapy reduces the risk of a bad outcome.</p> $\text{ARR} = \text{CER (control event rate)} - \text{EER (experimental event rate)}$
Relative Risk Reduction (RRR)	<p>Relative risk reduction (RRR) is the ratio of the absolute risk reduction (ARR) divided by the control event rate (CER).</p> $\text{RRR} = \frac{\text{CER} - \text{EER}}{\text{CER}}$
Absolute Risk Increase (ARI)	<p>Absolute risk increase (ARI) is the amount by which therapy increases the risk of one additional bad outcome.</p> $\text{ARI} = \text{EER (experimental event rate)} - \text{CER (control event rate)}$
Number Needed to Treat (NNT)	<p>Number needed to treat (NNT) is the number of patients that need to be treated for one to receive benefit. It can also represent the number of patients that need to be treated to prevent one additional bad outcome.</p> $\text{NNT}^* = 1/\text{ARR}$
Number Needed to Harm (NNH)	<p>Number needed to harm (NNH) is the number of patients that need to be treated for one additional bad outcome to occur (harm).</p> $\text{NNH}^* = 1/\text{ARI}$

\* If using percentage instead of proportion with ARR or ARI, divide into 100 instead of 1.<sup>1</sup>

# Key Points for Using NNTs

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## Number-needed-to-treat...

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- Can be used to evaluate benefit and risk for an individual patient, based on his/her values and preferences
- Can be calculated from raw data, OR, RRR and expected prevalence
- Is typically calculated for binary (dichotomous) outcomes – time-to-event outcomes require more complex calculations
- Is an estimate of effect size (should include a confidence interval as a reflection of precision)
- Should only be calculated from comparable studies with clinical homogeneity
- Should include the duration of treatment for the given effect
- Is more certain when calculated from rigorous systematic reviews or meta-analyses
- Is best when it is a small number (small number need treatment to see benefit)
- Is only applicable if current patient has similar characteristics to those in the study from which NNT is derived

# Sample Resources for NNT

URL Location	Description
<a href="http://www.ebem.org/nntcalculator.html">http://www.ebem.org/nntcalculator.html</a>	Calculator to derive NNT from 2X2 table data
<a href="http://www.cebm.net/index.aspx?o=1044">http://www.cebm.net/index.aspx?o=1044</a>	Table to derive NNT from OR
<a href="http://ktclearinghouse.ca/cebm/practise/ca/calculators/ortonnt">http://ktclearinghouse.ca/cebm/practise/ca/calculators/ortonnt</a> <a href="http://medcalc3000.com/NumberNeededToTreat.htm">http://medcalc3000.com/NumberNeededToTreat.htm</a>	Calculators to translate OR to NNT
<a href="http://www.medicine.ox.ac.uk/bandolier/Extraforbando/NNTextra.pdf">http://www.medicine.ox.ac.uk/bandolier/Extraforbando/NNTextra.pdf</a>	Chatelier's nomogram to determine NNT
<a href="http://www.ktclearinghouse.ca/cebm/glossary/nnt">http://www.ktclearinghouse.ca/cebm/glossary/nnt</a> <a href="http://www.thennt.com">http://www.thennt.com</a>	Websites of Published NNTs

Questions?

.....then on to the Workshop!