Epidemiology and Critical Appraisal
Interpreting Information from Clinical Trials. What are the Results? Part II

Objectives:

1. Differentiate between dichotomous and continuous outcomes.

2. When provided with information from a clinical trial develop a 2 x2 table.

3. When provided with information from a clinical trial calculate and interpret:

    - control event rate
    - experimental event rate
    - relative risk
    - relative risk reduction
    - absolute risk reduction
    - number needed to treat
    - odds ratio

4. Provide information regarding strengths and weaknesses of NNT.

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Measures of Association

- measures of association describe the strength of the relation between the intervention and outcome in clinical studies
- there are two types of measure:
    1. relative (for example relative risk reduction, odds ratio)
    2. absolute (event rates, absolute risk reduction, number needed to treat)
- in case-control studies only the odds ratio can be calculated because the incidence of the outcome can't be calculated from the data
- odds ratios are also used when combining data from a number of studies (as in meta-analysis) *and have useful statistical properties for techniques such as logistic regression*

Types of outcomes

1. dichotomous
    - these are 'yes' or 'no' outcomes
    - examples of dichotomous outcomes include dead or alive, stroke or no stroke, etc.

2. continuous
    - a variable that can theoretically take a number of values, with small differences between them
    - an example of a continuous outcome is blood pressure
    - sometimes continuous variables are treated as dichotomous – for example, an increase of 20% in exercise tolerance, or blood pressure lower than a threshold value

The 2 x 2 Table

		Outcome	
		Yes	No
Exposure	Yes (Present)	a	b
	No (Absent)	c	d

- the 2 x 2 table can be used to represent dichotomous data from a clinical trial (you will see a variation of this table used when we talk about diagnostic studies)
- remember that these data will reflect an effect at a given point in time, for example death at one year, or stroke at 5 years

Control event rate (CER):

- also known as baseline risk
- risk of an event in the control group of a clinical trial
- c + d is the total population in the control group
- CER = c / (c + d)

Experimental event rate (EER):

- risk of adverse event in experimental group or proportion of patients in experimental group that have event
- a + b is the total population of the experimental group
- EER = a / (a + b)

Absolute risk reduction (ARR):

- absolute difference between the risk of the event in the control and experimental groups
- ARR = CER – EER

Relative risk (RR):

- ratio of the risk of event in experimental group to risk in control group (or think of it as the proportion of original risk still present when patient receives the experimental therapy)
- relative risk = EER / CER

Relative risk reduction (RRR):

- reduction of adverse events in treatment group, relative to the proportion of events in the control group
- note that the RRR may be much larger and more impressive than the ARR, especially if the event rates are uncommon (this is the main disadvantage of the RRR, it does not reflect the magnitude of the risk without therapy)
- RRR = 1 – RR
- or RRR = ARR / CER

Number needed to treat (NNT):

- the number of patients one would need to treat to prevent one adverse event
- NNT = 1 / ARR (rounded upwards to nearest integer)
- number needed to harm (NNH) is applied to negative effects of treatment, using the absolute risk increase
- advantages of NNT include the fact that it is intuitive, simple to interpret, easy to calculate, and incorporates baseline risk
- problems with NNT include the fact that it cannot be used in isolation (to apply NNT to particular clinical situation factors such as patient age, adherence to therapy, costs etc. need to be considered)
- also, NNT needs to considered in context of time (for example death at one year, vs. 5 years) and it does not necessarily mean that none of the other patients receiving the treatment will not benefit in some way

Number needed to harm (NNH):

- number needed to harm (NNH) is calculated in the same way as NNT
- NNH = 1 / absolute risk increase (rounded to nearest integer)

Odds Ratio (OR):

- odds are a way of expressing probability – the probability that something will occur divided by the probability that it will not occur (or the number of events divided by the number of non-events)
- OR can vary from 0 (will never happen) to infinite (event will always happen)
- if the odds of an event are greater than 1 it is more likely to happen than not
- the odds ratio is calculated by dividing odds in treated group by odds in control group
    - odds in experimental group/odds in control group = (a/b) / (c/d) = ad / bc
    - because the OR can be estimated when the prevalence is not known it is used to measure effect in case-control studies
    - OR are also required for some statistical tests such as logistic regression, and are used in meta-analysis when combining data from different studies

- when events are rare risks and odds are similar; if event rate is high then the odds ratio will be much larger than the risk ratio

- OR = ad / bc (note this is cross multiplication on the 2x2 table)

- for some examples of OR please see the Appendix

Appendix I
Examples of Calculations

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7 percent vs. 65.3±11.4 percent), a lower lactate concentration (3.0±4.4 vs. 3.9±4.4 mmol per liter), a lower base deficit (2.0±6.6 vs. 5.1±6.7 mmol per liter), and a higher pH (7.40±0.12 vs. 7.36±0.12) than the patients assigned to standard therapy ($P \leq 0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0±6.3 vs. 15.9±6.4, $P<0.001$).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock.
NEJM 2001;345:1368.

2 x 2 Table: (using data from above trial)

		Outcome: In-Hospital Mortality	
		Yes	**No**
Exposure	**Yes** (Early Goal-Directed Therapy) N = 130	a 38	b 92
	No (Control) N = 133	c 59	d 74

Control Event Rate (CER):

- this is the baseline risk, and is the risk of mortality in the control group
- CER = c / (c + d) or 59 / 133 = 0.444 (or 44.4%)

Experimental Event Rate (EER):

- EER = a / (a + b) or 38 / 130 = .292 (or 29.2%)

Absolute Risk Reduction (ARR):

- ARR = CER – EER = .444 - .292 = .152 (15.2%)

Relative Risk Reduction (RRR):

- RRR = ARR / CER
- RRR = .152 / .444 = .342 (34.2%)

Number Needed to Treat (NNT):

- NNT = 1 / ARR = 6.6
- therefore we would need to treat 7 patients with goal-directed therapy to prevent one in-hospital death due to sepsis (remember we need to round up to the nearest integer for NNT)

Odds ratio:

- the odds are the number of events divided by the number of non-events
- for throwing a dice the probability of getting a '3' is 1 / 6; the odds of getting a '3' are 1 / 5
- for getting 'tails' on a coin the probability is 1 / 2, and the odds are 1
- if group A has a mortality of 25%, and group B has a 75% mortality the relative risk is 3, and the odds ratio is 9
- most of us find relative risk more intuitive
- note that when event rates are more common the odds ratio will be much larger than the relative risk; we need to be cautious when interpreting odds ratios that we do not use them as an approximation of relative risk if event rates are high

- for our example:
  - OR = ad / bc = (38 x 74) / (92 x 59) = 0.52