# Skills required to make sense of a summary

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**UPN 475-000-09-017-L04-P**

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European Association of Hospital Pharmacists

# No conflicts of interest to declare

# What I want to cover

- How to make sure we read only what we need to read
- How to make sense of what we read in summaries
  - How big the effect was
  - How trustworthy the results are

# First - A word from Monty Hall


- You have reached the final of *Lets make a deal*
- You are offered a choice of three doors, behind one is a car, behind each of the other two is a goat
- You make your choice, but before you open it, Monty opens one of the other doors and shows a goat
- He offers you the chance to change your mind and choose a different door.
- **Are you more likely to win the car if you do?**


1. I’ve seen this before
2. You are **more** likely to win if you change your mind
3. You are **less** likely to win if you change your mind
4. It **makes no difference** whether you change your mind or not
5. Don’t know
6. I want to win a goat

# And the answer is...

2


- Your chance of winning doubles from 1 in 3 to 2 in 3 if you change your mind
- The correct answer may not be the obvious answer
- www.grand-illusions.com/monty.htm

# Skills required to sift the good evidence from the not so good

- How do we locate the best evidence?
- What are the reliable sources?
- How do we decide?
- How do we interpret the important bits?
- What if someone gives you some ‘new’ evidence?

# What are the criteria used when looking for the best answer or important evidence?

Slawson DC and Shaughnessy AF. J Am Board Fam Pract 1999; 12: 444-9

$$\text{Usefulness} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work}}$$

# How can we *quickly* spot what is NOT important to us?

- Not **RELEVANT**
  - Upstream to clinical decisions being made, e.g. animal or *in vitro* studies
  - Study populations and / or settings do not reflect question type, practice population and settings
- Not **VALID**
  - Poor study design
  - Bias and confounding
  - Measurement validity
  - Insufficient power

# So, filtering for *relevance*

- **F**easible (intervention)
- **O**utcomes (patient-orientated)
- **C**ommon (condition)
- **C**hange in practice required

# What you measure matters – POOs and DOOs

## Patient Oriented Outcomes:

- Reduces heart attacks and strokes
- Reduces diabetic foot ulcers
- Reduces night time awakenings

## Disease Oriented Outcomes:

- Reduces blood pressure
- Improves HBA1c
- Improves PEF

***If the answer to <u>any</u> of those is "no"***

# I don't know and I don't care

# After checking it is relevant, is the answer likely to be *valid?*

- How to quickly spot the *fatal flaws:*
  - Is it a high level of evidence?
  - Is it statistically significant?
  - Is it clinically significant?:
    - Do you understand what the the numbers tell you?
    - Absolute vs. relative risk vs. NNT
  - Was there enough people in the study for long enough?
  - Was the allocation concealed?

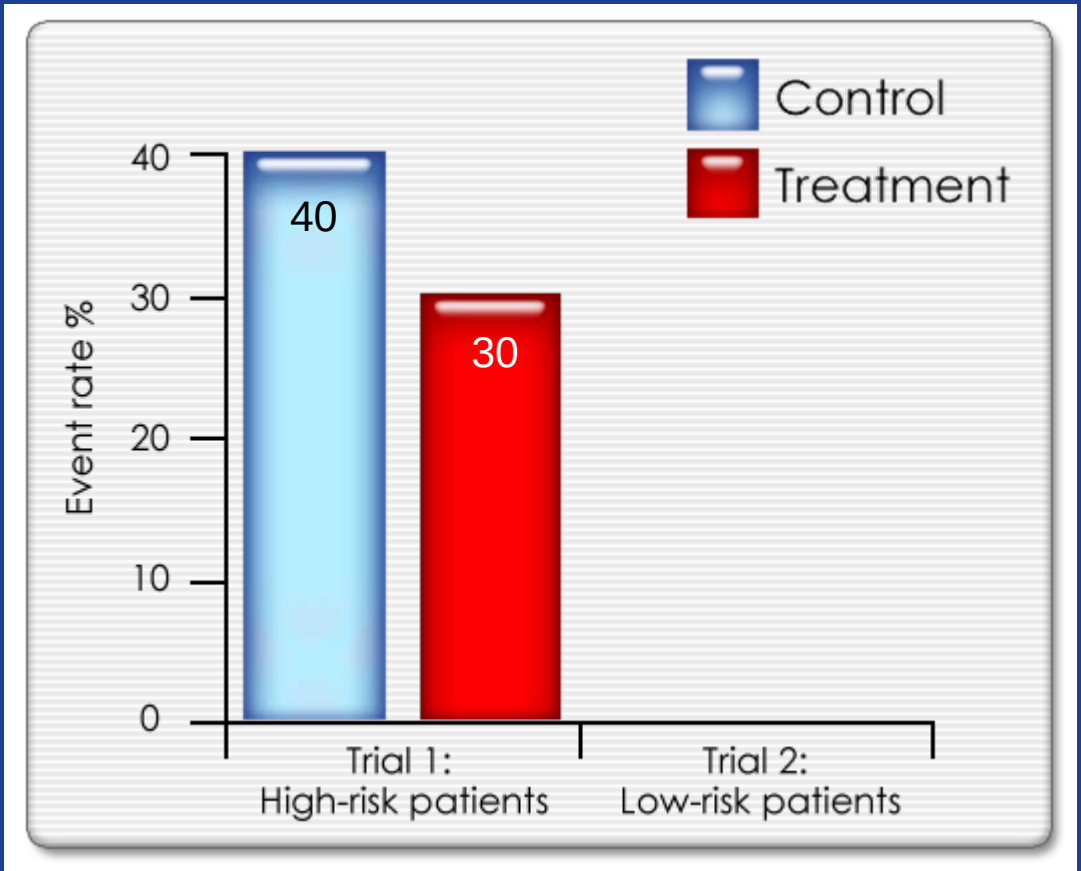
- A clinical trial recruited people with multiple CV risk factors and compared Exatide with placebo. After 3 years' treatment, the rate of death or non-fatal MI was 30% in the Exatide group and 40% in the placebo group.
- What was the **relative risk reduction** in death or non-fatal MI with Exatide compared with placebo?

1. 10%
2. 25%
3. 0.75
4. 75%
5. Don't know

- A clinical trial recruited people with multiple CV risk factors and compared Exatide with placebo. After 3 years' treatment, the rate of death or non-fatal MI was 30% in the Exatide group and 40% in the placebo group.
- What was the **absolute risk reduction** in death or non-fatal MI with Exatide compared with placebo?

1. 10%
2. 25%
3. 0.75
4. 75%
5. Don't know

# In pictures……..


Control
Treatment
Event rate %
40
30
20
10
0
40
30
Trial 1:
High-risk patients
Trial 2:
Low-risk patients

**40%** of people taking the control (placebo) died or had a non-fatal MI. Only **30%** of people taking the treatment (Exatide) died or had a non-fatal MI

- Absolute risk reduction (risk difference):
  - "How many fewer patients experienced the endpoint in the treatment group than in the control group?"
- Control rate – experimental rate = 40% - 30% = 10%

- Relative risk reduction:
  - "By how much did treatment reduce the chance of the endpoint occurring in the treatment group compared with the control group?"
- (Control rate – experimental rate) / control rate = 10% / 40% = 1/4 = 25%

- A clinical trial recruited people with multiple CV risk factors and compared Exatide with placebo. Over 3 years, the rate of death or non-fatal MI was 30% in the Exatide group and 40% in the placebo group.
- What was the **number needed to treat** with Exatide compared to placebo to prevent death or non-fatal MI?

1. 10
2. 20
3. 30
4. 40
5. Don’t know

- Number needed to treat
  - "How many people, on average, do we need to treat for one of them to benefit?"

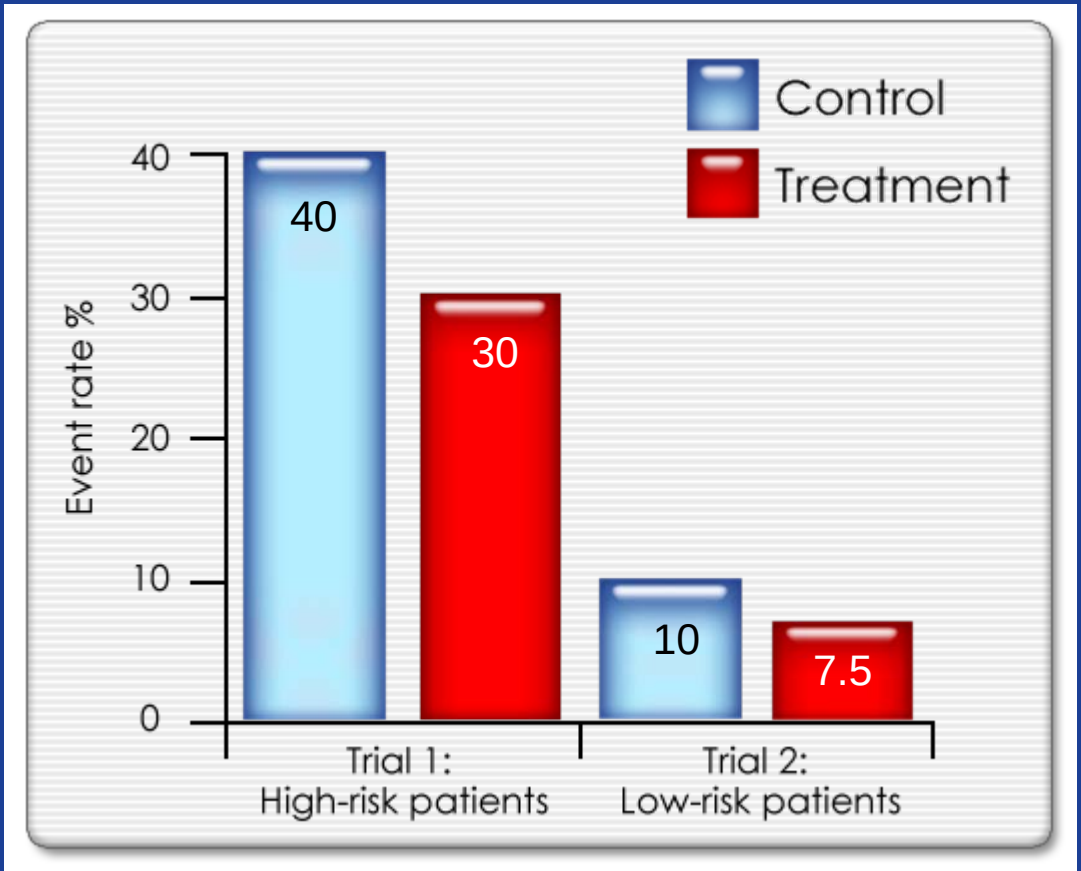
NNT=100/ARR(%):

- In this case 100/10 = **10**
- For every 10 people who takes the treatment, one benefits who wouldn't have done had they all taken control.
- Each of the other 9 die or have non-fatal MIs, or do not die or have non-fatal MIs, just as would have happened if they had taken control


- A clinician is considering using Exatide in a patient at lower risk of death or non-fatal MI than those in the trial. This patient's risk is about 10% over 3 years.
- Assuming the relative risk reduction is the same (25%), what is this patient's **absolute** chance of benefiting from treatment?

1. Greater than the people in the trial
2. Same as the people in the trial
3. Less than people in the trial
4. Don't know

# In pictures…….


Control
Treatment
Event rate %
40
30
20
10
0
40
30
10
7.5
Trial 1:
High-risk patients
Trial 2:
Low-risk patients

- Baseline risk is 10%
- Exatide reduces this by 25%
- Risk in treatment group is 7.5%
- ARR is 2.5%
- NNT is 100/2.5 = 40
- So this patient has only a 1 in **40** chance of benefiting

# And relative risk?

- Ratio of risk (or rate) in intervention group to risk (or rate) in control group
- In first trial = 30% / 40% = 0.75
- In second trial = 7.5% / 10% = 0.75
- RRR = 1-RR
- If RR **<** 1, the event is **less** likely with the intervention
- If RR **>** 1, the even is **more** likely with the intervention

# EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

N Engl J Med 2001; 345: 494-502.

**P**opulation: patients with acute coronary syndrome at low risk of bleeds

**I**ntervention: clopidgrel (plus aspirin)

**C**omparison: placebo (plus aspirin)

**O**utcomes:

# EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

THE CLOPIDOGREL IN UNSTABLE ANGINA TO PREVENT RECURRENT EVENTS TRIAL INVESTIGATORS*

N Engl J Med 2001; 345: 494-502.

The primary outcome – a composite of death from CV causes, nonfatal MI or stroke – occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group (RR 0.80, 95% CI 0.72 to 0.90; P<0.001)

There were significantly more patients with major bleeding in the clopidogrel group than the placebo group (3.7% versus 2.7%, RR 1.38; P=0.001)

# Conclusions

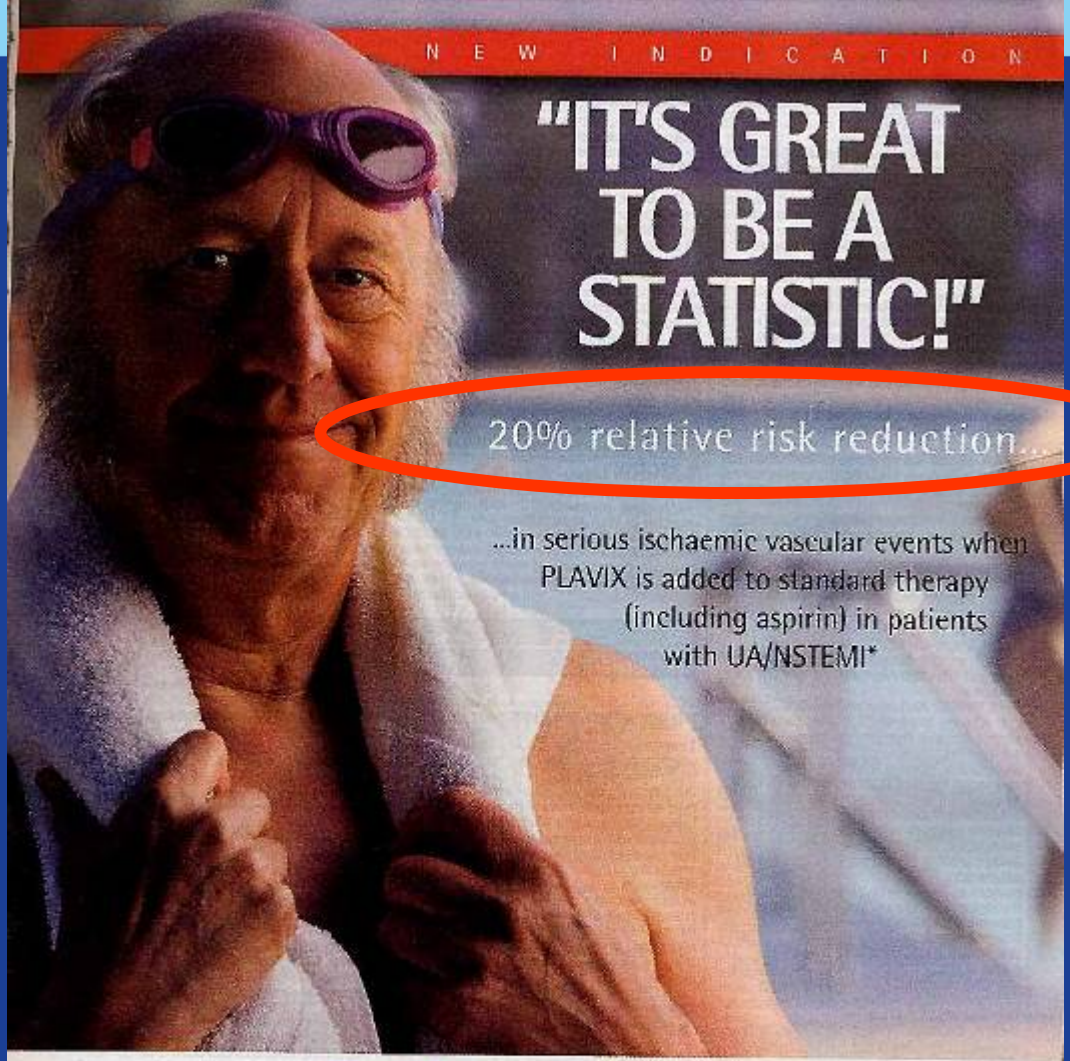
Clopidogrel significantly reduces the risk of:

a) CV Death, MI, Stroke by about one-fifth ($P < 0.001$)

b) CV Death, MI, Stroke, and Refractory Ischemia by about one-sixth ($P < 0.001$)

c) Early revascularization, severe and recurrent ischemia and heart failure by about one-fifth to one-quarter in hospital

There is a small (absolute 1%) significant excess of major, but not life threatening, bleeds




Plavix®

clopidogrel 75mg

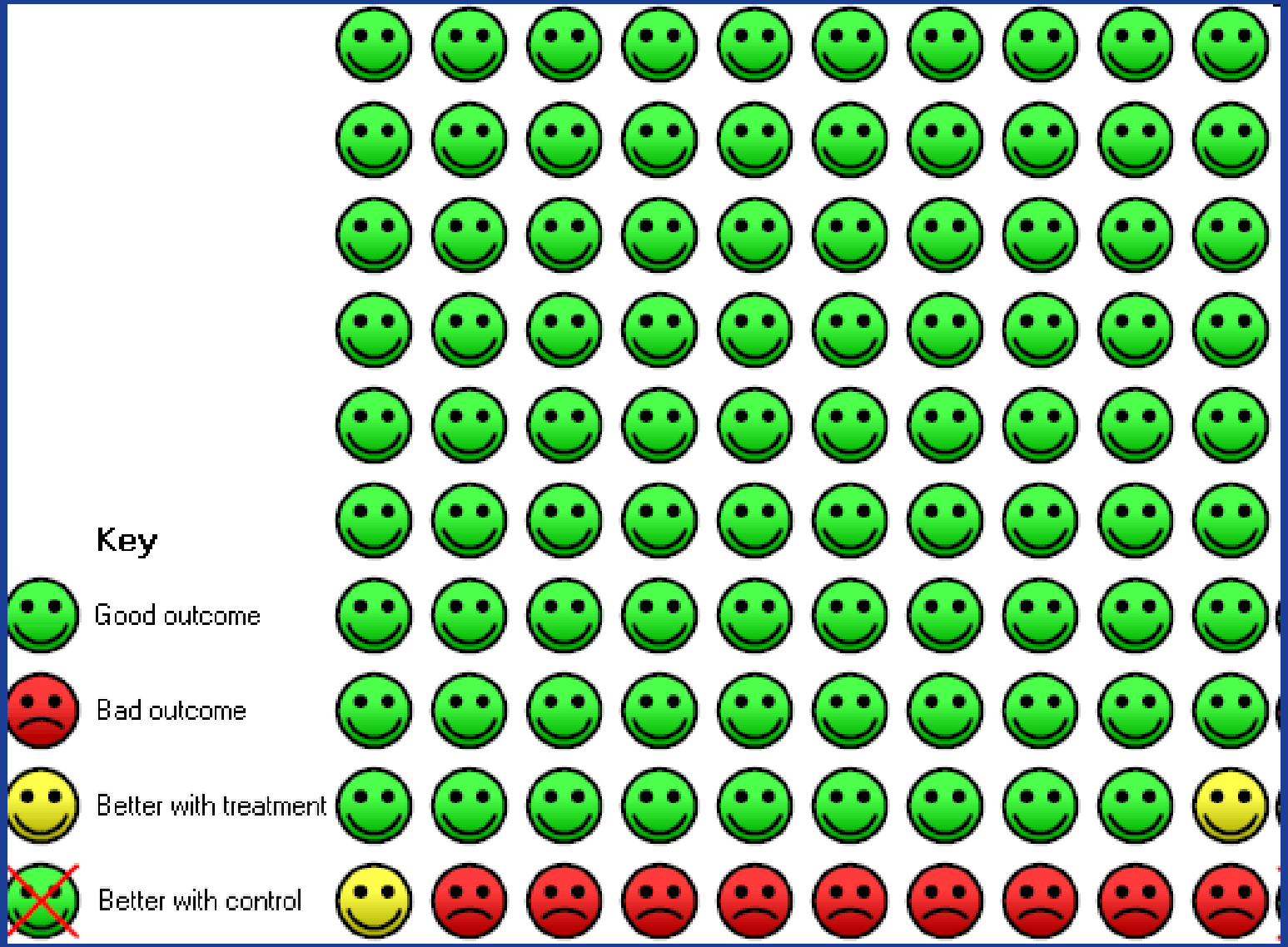
Because prevention is better with CURE

POM

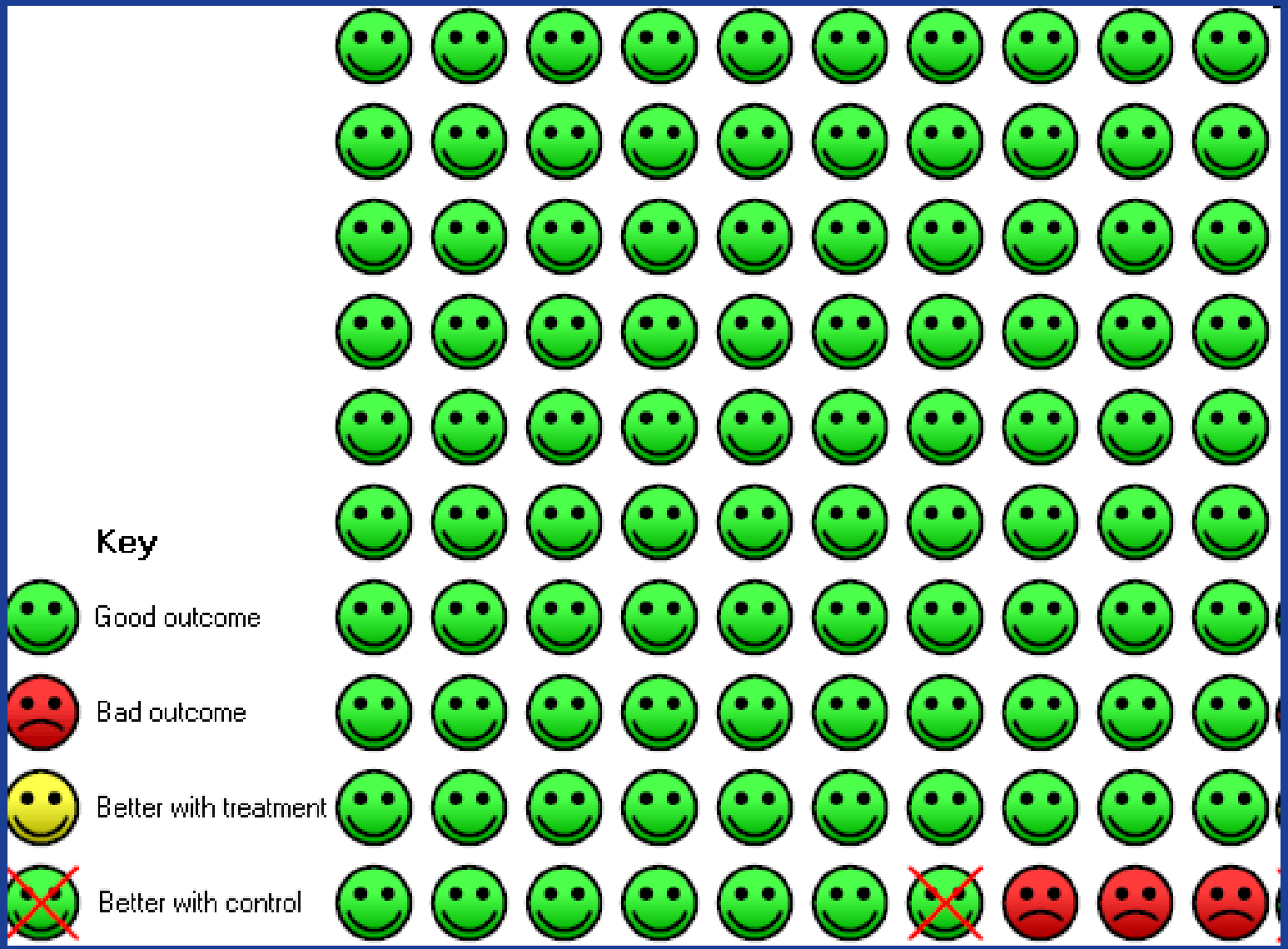
Further information is available on request from Sanofi-Synthelabo, One Onslow Street, Guildford, Surrey GU1 4YS.
Date of preparation: September 2002.

* 20% RRR in MI/stroke/CV death.
Unstable angina/Non-ST-elevation myocardial infarction.

# Death from CV causes, nonfatal MI or stroke



# Major bleeds



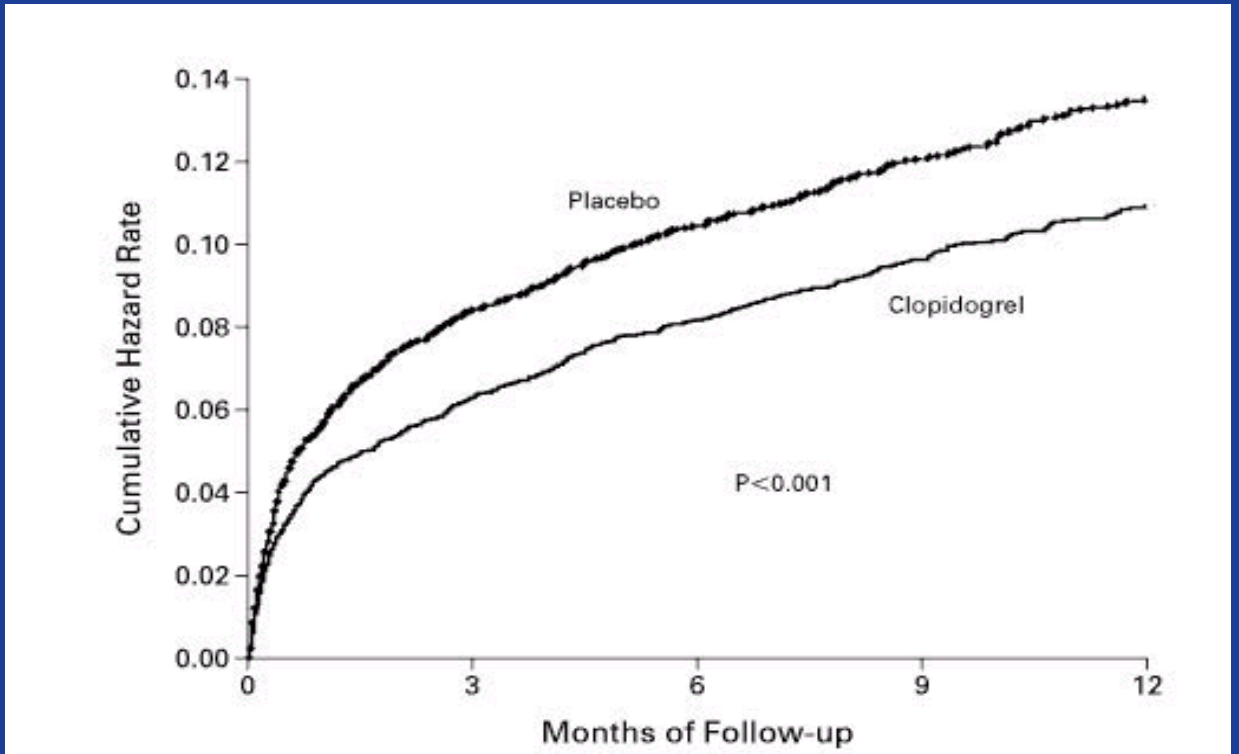
**Explain these results to your neighbour as though she/he were a patient with ACS**

# So what have we been saying?

- Relative risk reduction always looks more impressive, but on it's own it can be misleading.
- Absolute risk reduction and NNTs give the benefit in the population.
- So if applying evidence from a RCT to an individual patient we MUST consider:
  - is **my** patient at the same risk as the average patient in that trial?
  - If at lower risk (younger, fitter, etc.), the NNT would be bigger, but all would be at risk of side effects.
    - Baseline risk high = lots benefit
    - Baseline risk low = few benefit

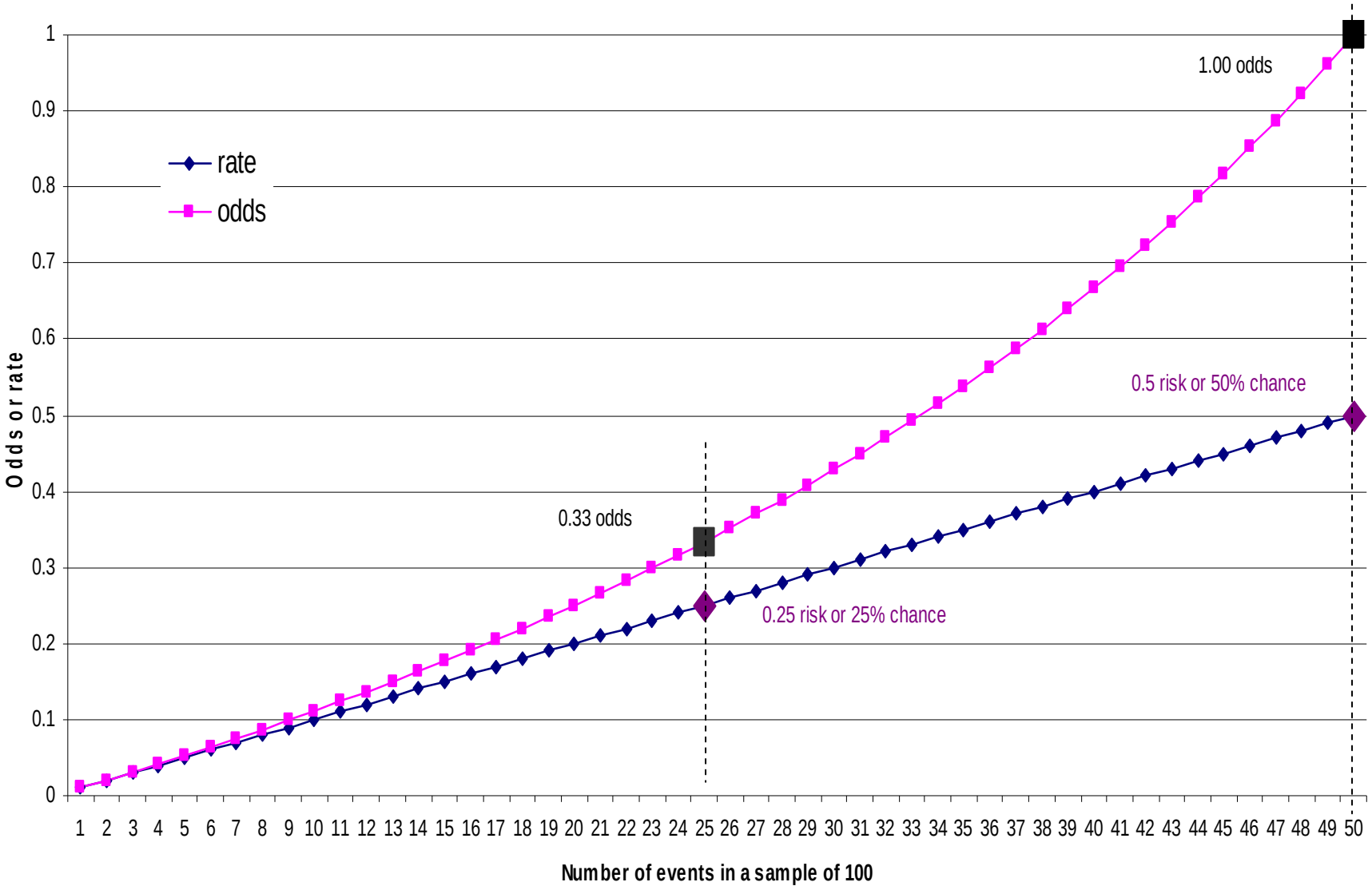
# Hazard ratios and odds ratios

# Survival curves and hazard ratios



# Odds and Odds Ratio

- Odds = events/non-events
- Odds ratio = ratio of odds in two groups
- As the baseline risk increases, the odds increases compared to the risk (or rate)
- That means that
  - the OR reduces compared to the relative risk
  - The odds ratio reduction is increases compared to the relative risk reduction (and looks more impressive)


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Odds or rate
rate
odds
1.00 odds
0.5 risk or 50% chance
0.33 odds
0.25 risk or 25% chance
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50
Number of events in a sample of 100

# Summary so far

- With regard to information, the job of health professionals is to become skilled at locating **relevant, valid** data for their needs and applying it to their practice
- We can screen for relevance quickly and easily
  - FOCC mnemonic
  - Think POOs, not DOOs
- Consider relying on trustworthy sources to screen for validity
- The relative risk and relative risk reduction are constant
- The absolute benefits (e.g. NNT) depend on the baseline risk
  - The lower the baseline risk, the lower the absolute benefits (and the greater the NNT) for any given relative risk reduction
- We need to use absolute and relative terms consistently

**So, we've minimised biases and got a study result**

How can we trust the results?

# The Sacred P-Value

**P< 0.05**

- A clinical trial recruited people with multiple CV risk factors and compared Exatide with placebo.
- After 3 years treatment, the **relative reduction** in **risk** of death or non-fatal MI with Exatide compared with placebo was 25% (P<0.05)
- What does this P value tell us?

1. It confirms that Exatide has a big relative effect on risk
2. It means that Exatide is likely to work in more than 95% of people
3. It tells us that there is a 5% possibility that this difference was just due to chance
4. All of the above
5. Don’t know

# P Value

- "***P***robability" level
- The likelihood that the difference observed between two interventions could have arisen by **chance**
- Arbitrarily set at 1 in 20, i.e.
  - P = 0.05, or
  - 5% risk

# Would you always take a treatment that had been shown to be effective statistically?

# P Value

- Depends on several factors
  - How **large** the effect was
  - How **consistent** the effect was
  - How **many** patients were studied
- As all of these factors increase, the likelihood of finding statistical significance increases

**BUT, REMEMBER,**

- Once we've decided the difference was **NOT** due to chance, we have to decide on the **clinical** significance

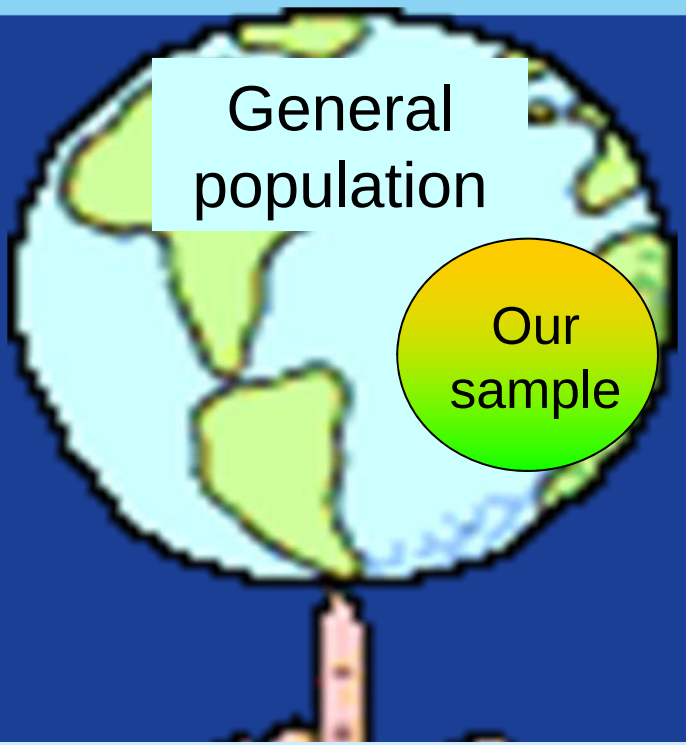
# Clinical vs. statistical significance

- Outcome measured – how long does it takes to walk 50 feet?
  - What would you say was a clinically meaningful difference?
    - ✓ 3minutes?
    - ✓ 1 minute?
    - ✓ 10 seconds?
- In two studies the difference in time to walk 50 feet (15 metres) in those given NSAIDs and those given paracetamol was……..

Less than 0.7 seconds (but P<0.001)

50 feet

# Confidence Intervals




*Confidence intervals are the range of values between which we could be 95% certain that this result would lie if this intervention was applied to the general population*

# Confidence Intervals

## Estrogen Replacement Therapy in Women with a History of Proliferative Breast Disease

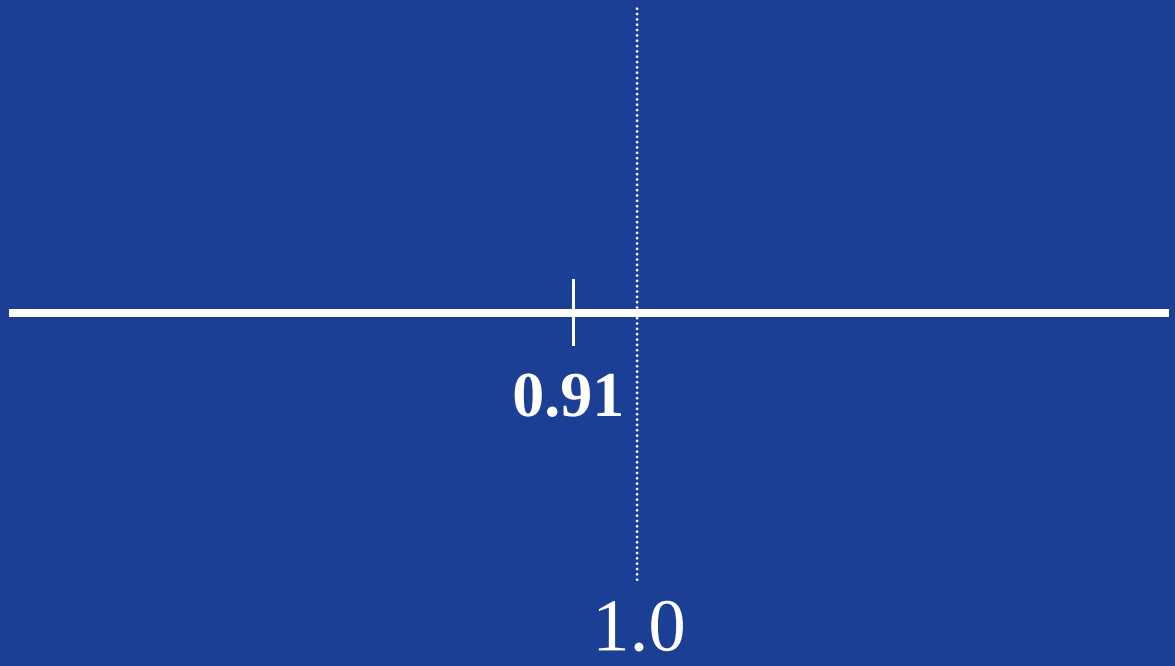
**TABLE 4**
**Relative Risk of Invasive Breast Carcinoma Associated with Duration of Estrogen Replacement Therapy in Menopausal Women with a History of Premenopausal Benign Breast Disease**

| Estrogen replacement therapy | No. of patients | No. of woman-years | No. of breast carcinomas | Relative risk[a] (95% confidence interval) |
|---|---|---|---|---|
| Unknown | 402 | 3952 | 18 | 1.44 (0.87-2.4) |
| Yes, duration | 3383 | 39,509 | 107 | 0.91 (0.68-1.2) |
| 1-12 mos | 707 | 9221 | 26 | 1.00 (0.65-1.6) |
| 1-5 yrs | 888 | 14,028 | 29 | 0.78 (0.51-1.2) |
| >5 yrs | 1779 | 16,063 | 52 | 0.98 (0.69-1.4) |
| Unknown | 9 | 197 | 0 | 0.0 |
| No | 2028 | 28,154 | 88 | 1.0[b] |
| Total | 5813 | 71,615 | 213 | |

# Confidence Intervals

## Estrogen Replacement Therapy in Women with a History of Proliferative Breast Disease

| | | | | |
|---|---|---|---|---|
| Yes, duration | 3383 | 39,509 | 107 | 0.91 (0.68–1.2) |



# Confidence Intervals

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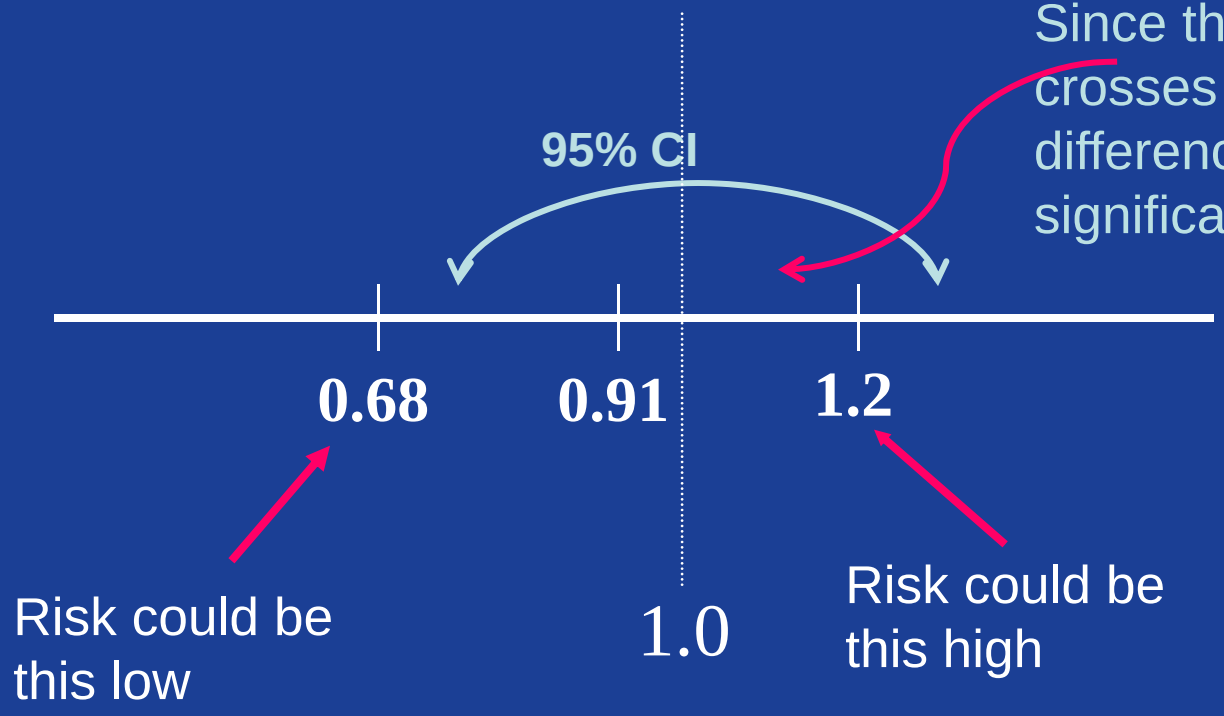


# Tell me again about P and CI?

- Statistical significance is not the “truth”
- Statistical significance is a requirement for determining clinical significance, but is not enough to *signify* a clinical difference
- The P value tells us the probability that the difference between two treatments was due to chance
- Confidence intervals help us to understand how close our estimate is to the “truth”

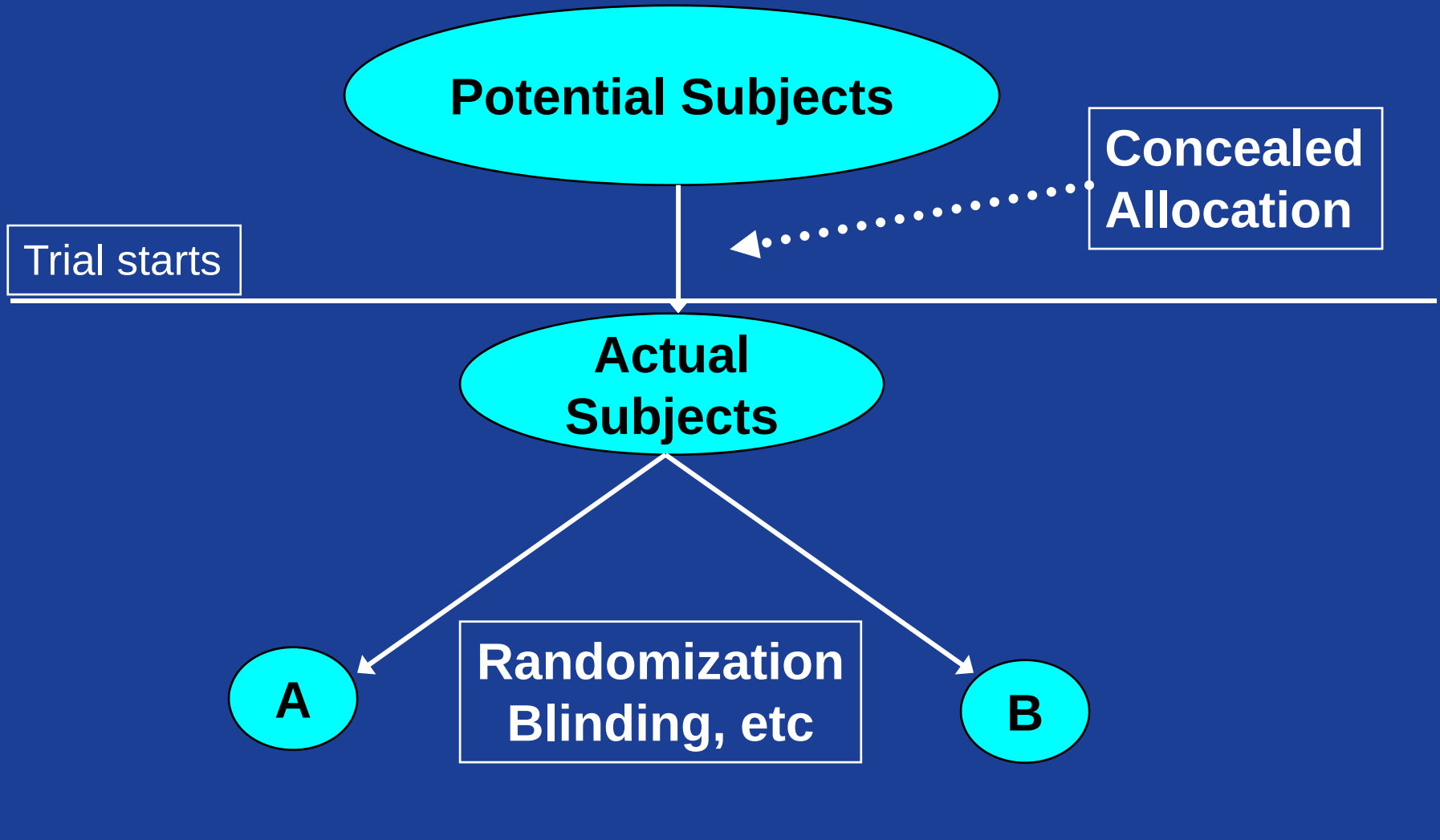
**Finally when determining validity –**

# Allocation Concealment

# Was allocation assignment "concealed"?

- Did investigators know to which group the potential subject would be assigned before enrolling them?

# Conducting a Study



# Importance of concealed allocation

Schulz KF, et al. JAMA 1995; 273: 408-12
Schulz KF and Grimes DA. Lancet 2002; 359: 614-8

- Trials with unconcealed allocation consistently overestimate benefit by ~40%
- Having a randomised (unpredictable) sequence should make little difference without adequate allocation concealment
- Investigators admitted:
  - altering enrolment or allocations ….. after decoding future assignments, which were ….. visible through translucent envelopes held up to bright lights
  - opening unsealed assignment envelopes
  - sensing the differential weight of envelopes
  - opening unnumbered envelopes until they found a desired treatment

# So what have we been saying? - 1

- With regard to information, the job of health professionals is to become skilled at locating **relevant, valid** data for their needs and applying it to their practice
- We can screen for relevance quickly and easily
  - FOCC mnemonic
  - Think POOs, not DOOs
- Consider relying on trustworthy sources to screen for validity
- Everyone needs to understand the basic language used in summaries

# So what have we been saying? - 2

- Relative risk reduction always looks more impressive, but on it's own it can be misleading.
- Absolute risk reduction and NNTs give the benefit in the population.
- So if applying evidence from a RCT to an individual patient we MUST consider:
  - is **my** patient at the same risk as the average patient in that trial?
  - If at lower risk (younger, fitter, etc.), the NNT would be bigger, but all would be at risk of side effects.
    - Baseline risk high = lots benefit
    - Baseline risk low = few benefit

# So what have we been saying? - 3

- Statistical significance is a requirement for determining clinical significance, but is not enough to *signify* a clinical difference
- The P value tells us the probability that the difference between two treatments was due to chance
- Confidence intervals help us to understand how close our estimate is to the “truth”
- If allocation was not concealed, the benefits could be hugely overestimated