



USING RESULTS GATHERED FROM MANY TO INFORM DECISIONS ABOUT INDIVIDUALS

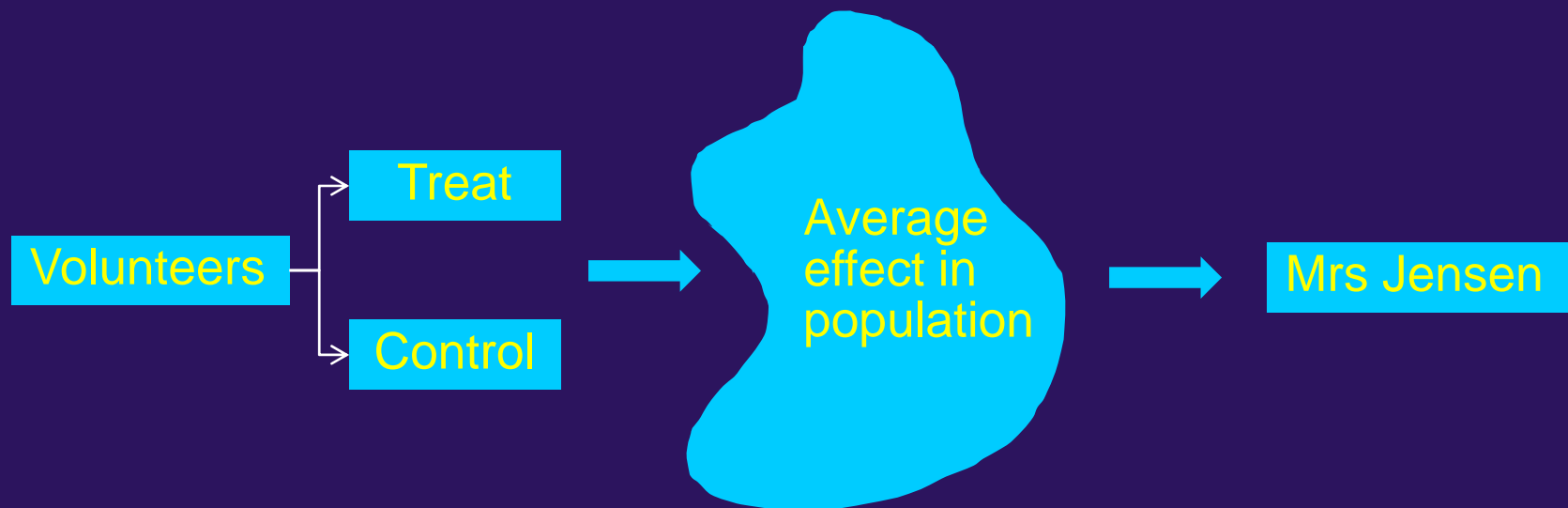
Rob Herbert

Using data from clinical trials

**Study
sample**

**Hypothetical
population**

Patients



Three (big) questions

1. Is there any real value in knowing the average effect of intervention?
2. How much variation is there, between-people, in the effects of intervention?
3. How can we recommend intervention only to those who will benefit?



Are *average* effects of any real interest?

- Most clinical trials usually only tell us about the *average* effects of intervention in a population
- The *average* effect of intervention in a population is the *expected* effect for any individual from that population. So randomised trials provide estimates of the expected effect of intervention on individuals



Three (big) questions

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Yes. It's a pretty good start.

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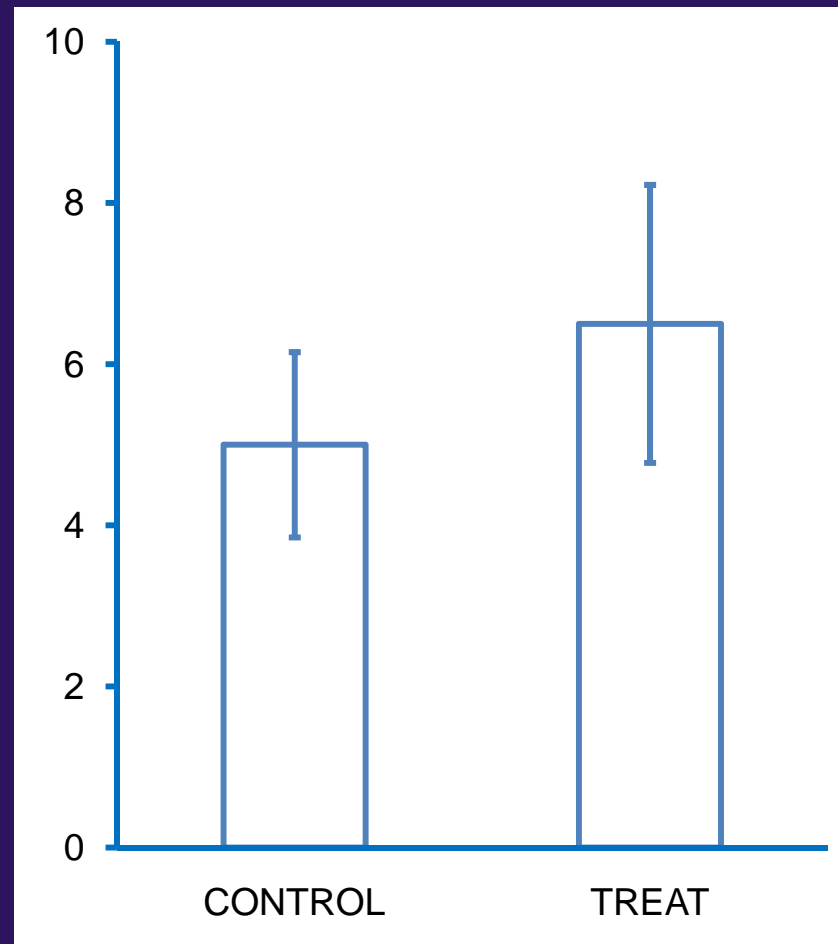


How much do treatment effects vary?

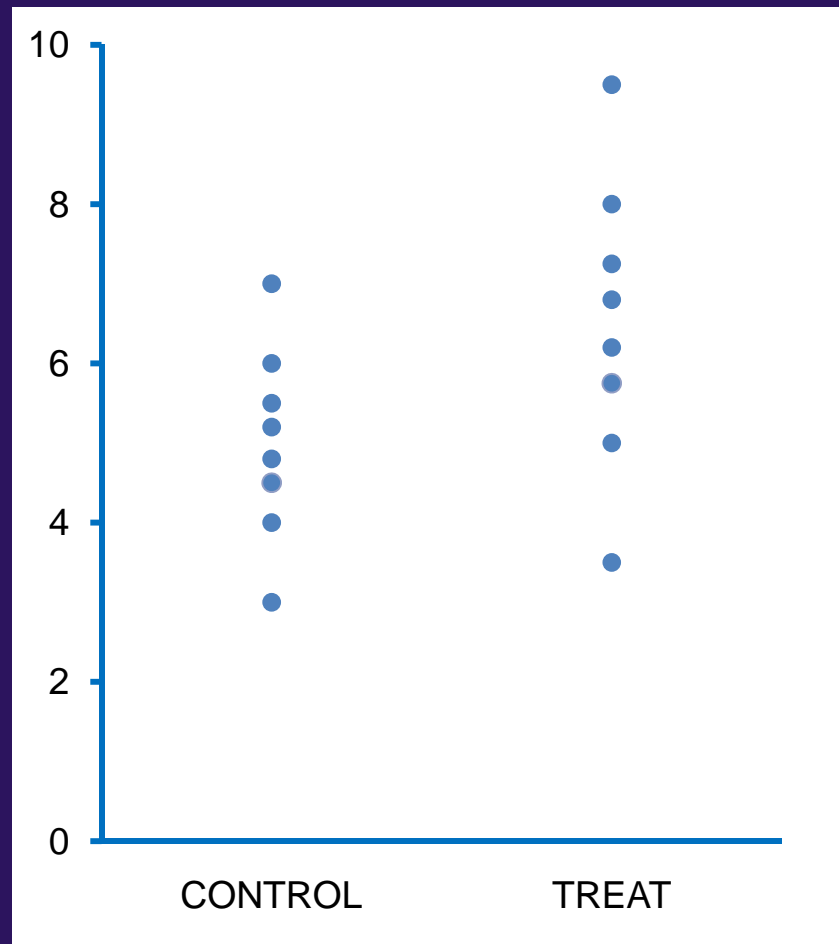
- It would be useful to know how much the effects of intervention vary from person to person
- Clinical observation can't tell us about variability of effects of intervention
- Maybe we can estimate variability of effects using data from randomised trials?



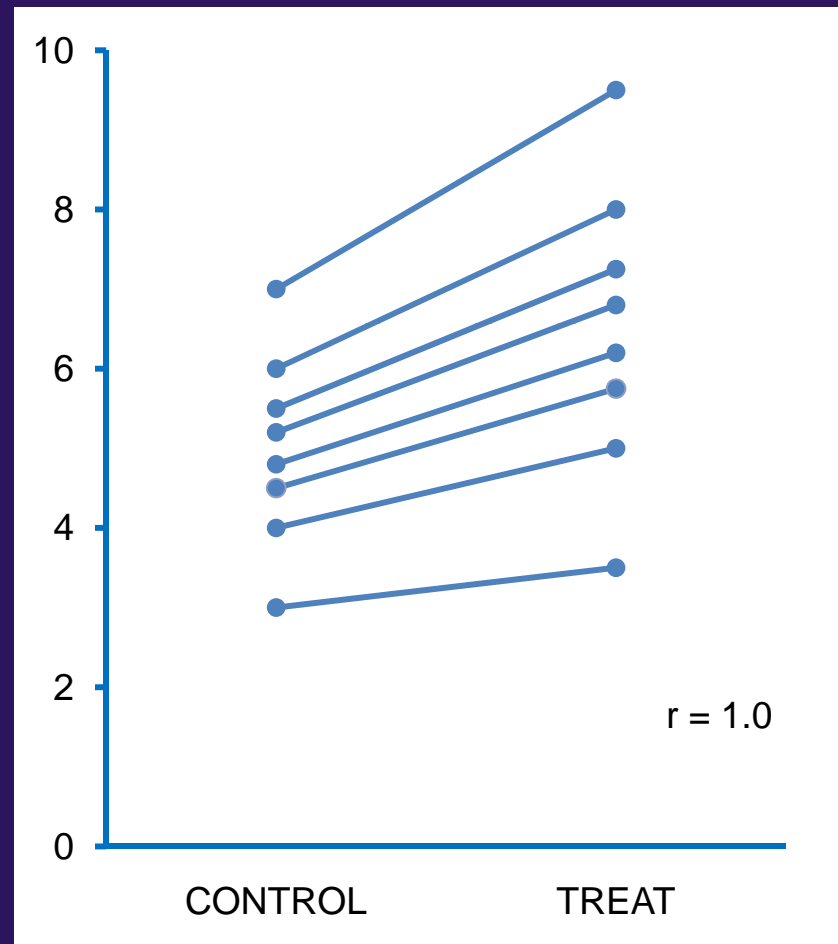
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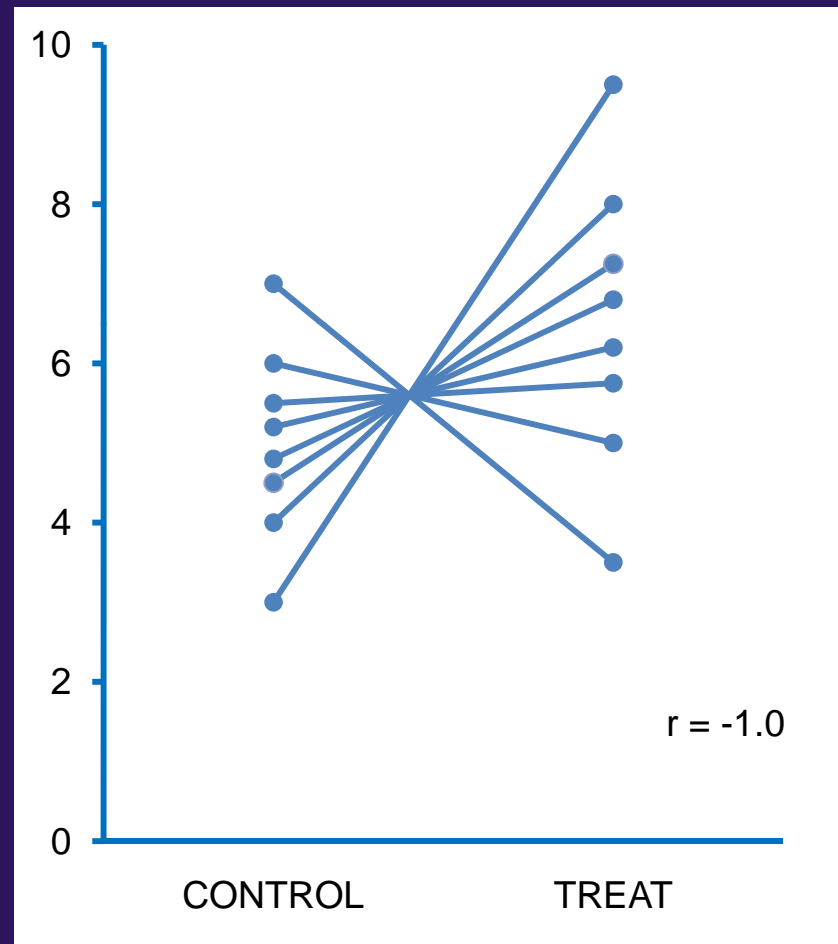
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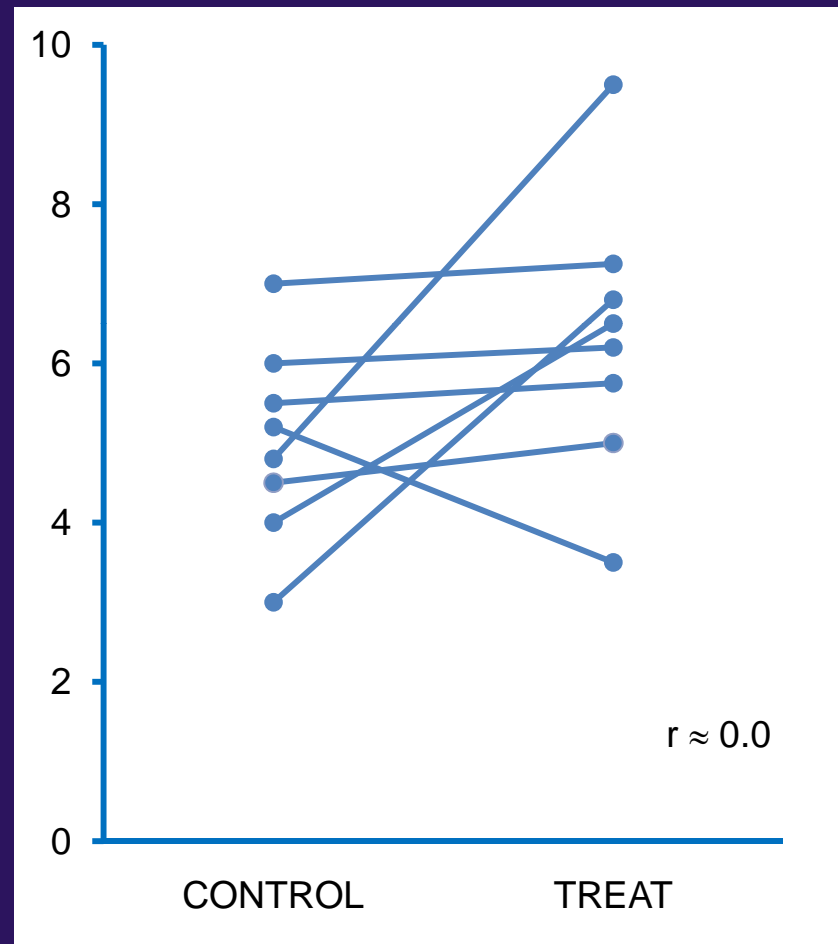
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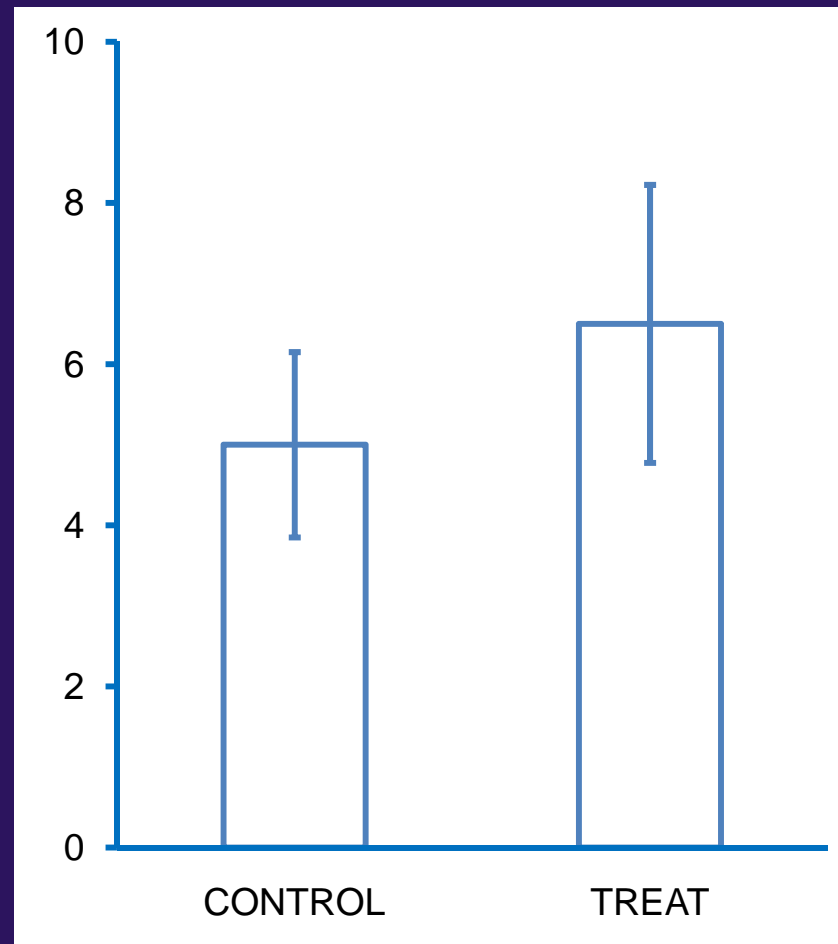
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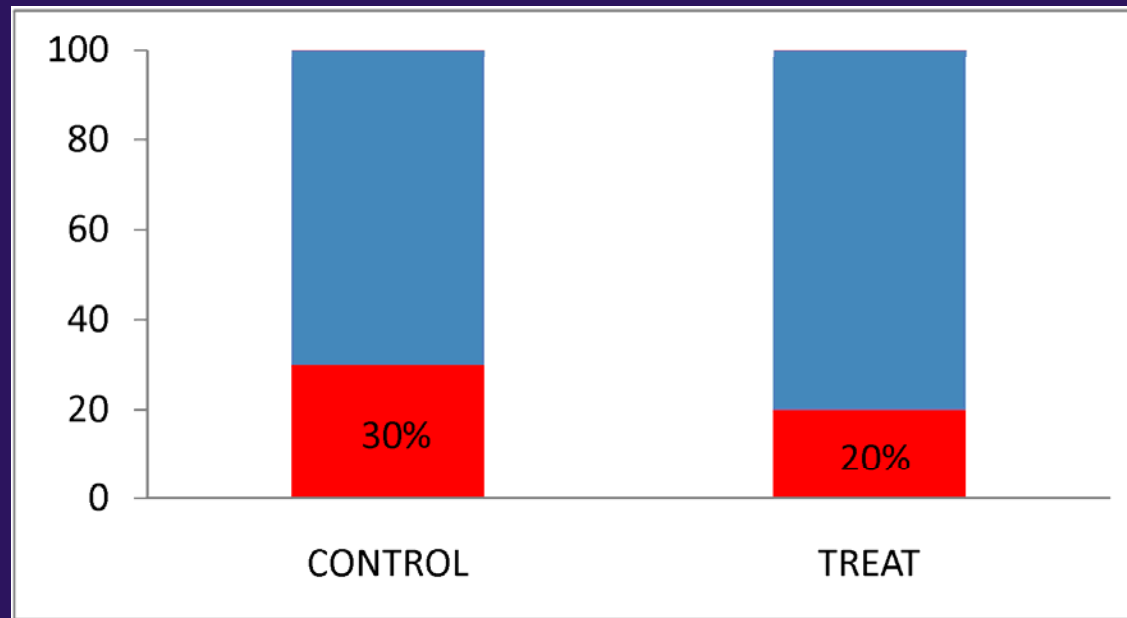


How much do treatment effects vary?

- It is hard to quantify person-to-person variability in effects of intervention because, in most trials with continuous outcomes, we have no way of determining if the size of the effect of intervention depends on what the outcome would have been without intervention
- A similar problem arises in trials with binary outcomes ...



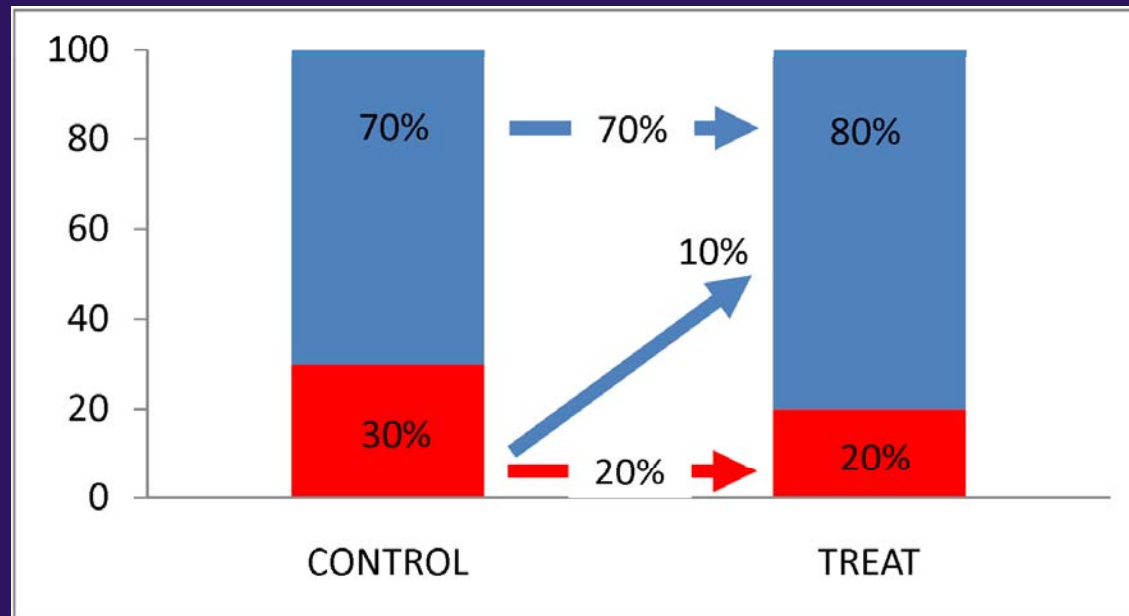
How much do treatment effects vary?



NNT = 10



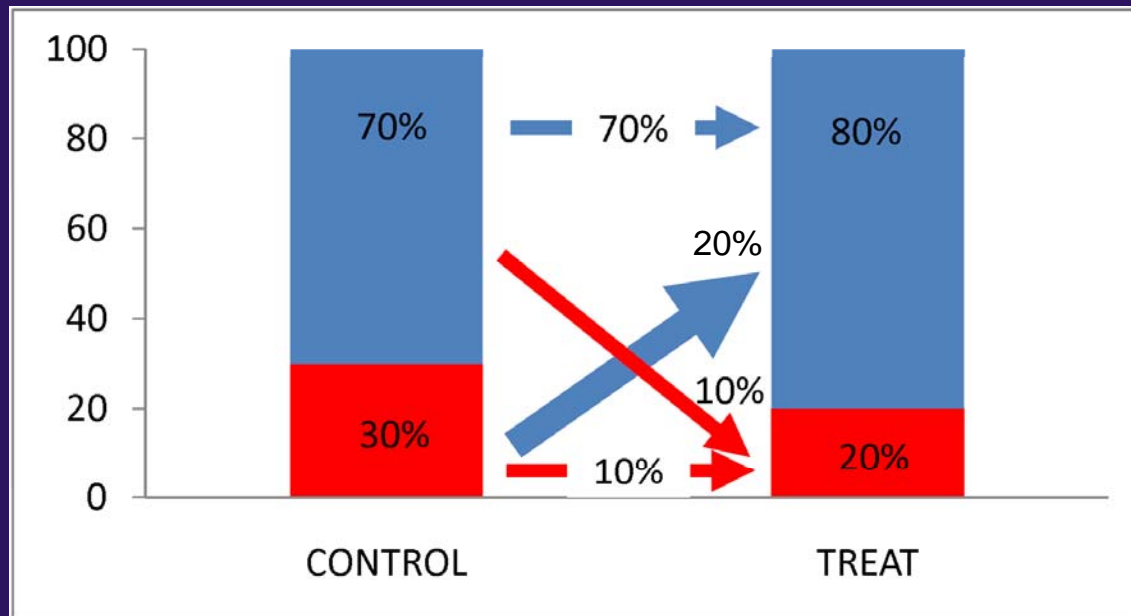
How much do treatment effects vary?



NNT = 10



How much do treatment effects vary?



(average) NNT = 10

Patient level NNT = 5, NNH = 10



How much do treatment effects vary?

- Randomised trials can give us good estimates of the average (expected) effect of intervention, but they give us little information about the amount of person-to-person variability in effects of intervention



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Hmmm. It's hard to know.

3. How can we recommend intervention only to those who will benefit?



Can we intervene selectively?

- Sometimes “subgroup analyses” are conducted on data from randomised trials to identify people who respond best to intervention
- Subgroup analyses are prone to spurious findings



RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2

ISIS-2 (SECOND INTERNATIONAL STUDY OF INFARCT SURVIVAL) COLLABORATIVE GROUP*

Summary 17 187 patients entering 417 hospitals up to 24 hours (median 5 hours) after the onset of suspected acute myocardial infarction were randomised, with placebo control, between: (i) a 1-hour intravenous infusion of 1.5 MU of streptokinase; (ii) one month of 160 mg/day enteric-coated aspirin; (iii) both active treatments; or (iv) neither. Streptokinase alone and aspirin alone each produced a highly significant reduction in 5-week vascular mortality: 791/8592 (9.2%) among patients allocated

expected. For example, subdivision of the patients in ISIS-2 with respect to their astrological birth signs appears to indicate that for patients born under Gemini or Libra there was a slightly adverse effect of aspirin on mortality (9% SD 13 increase; NS), while for patients born under all other astrological signs there was a strikingly beneficial effect (28% SD 5 reduction; $2p < 0.00001$). It is, of course, clear



Can we intervene selectively?

- Subgroups provide a hazardous way of determining who does and does not benefit from an intervention
- Is there any other way we can target intervention at the people who will benefit most? ...



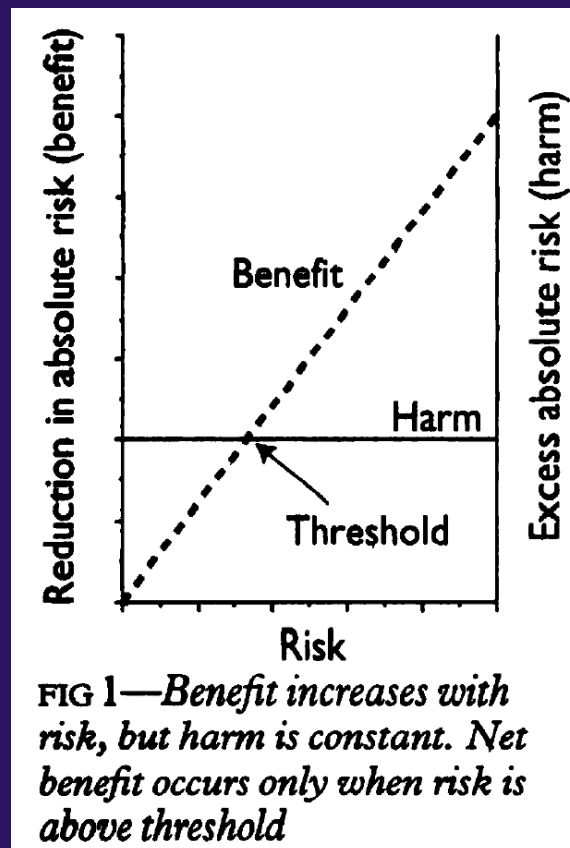
Can we intervene selectively?

- A. Use common sense to “adjust” estimates of effect, obtained from randomised trials, based on patient characteristics



Can we intervene selectively?

B. Target people who have serious disease



Can we intervene selectively?

C. Target people who would be happy with even small effects of intervention

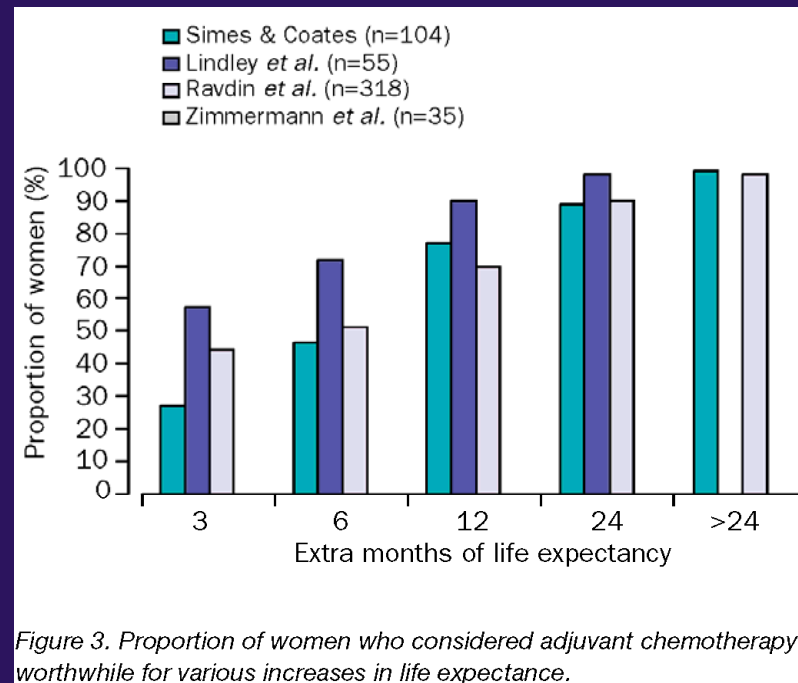
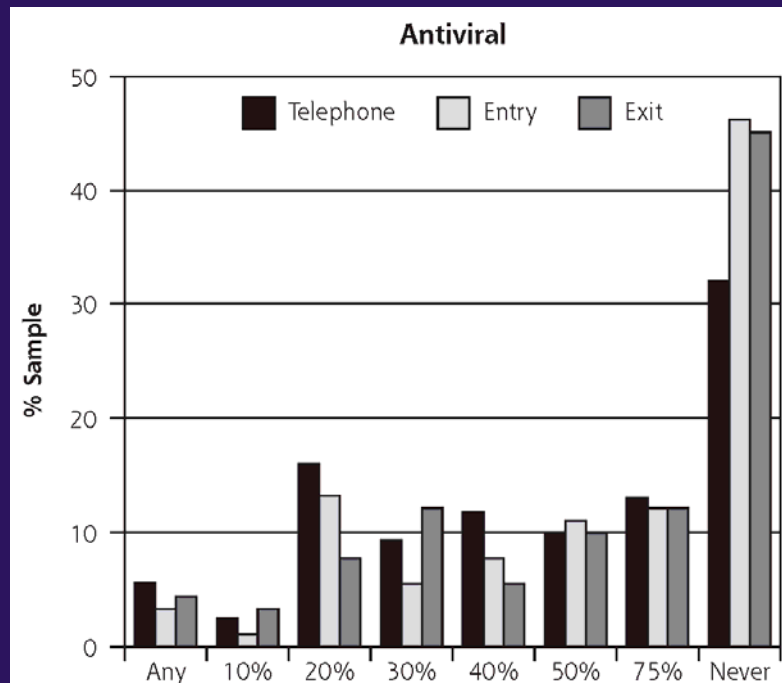


Figure 3. Proportion of women who considered adjuvant chemotherapy worthwhile for various increases in life expectancy.



Can we intervene selectively?

- D. When intervention is ongoing, consider monitoring outcomes
- We should be most swayed by clinical measures of outcome when the trials are weak, and when clinical measures are direct and reliable, and show large effects



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Three (big) questions

3. How can we recommend intervention only to those who will benefit?

Use common sense, not subgroup analyses, to “adjust” trial-based expectations of effect for patient characteristics

Target people with serious disease and people who will be satisfied with even small effects

Monitor outcomes, but interpret data cautiously

