Balancing the importance of getting some information *vs.* the importance of getting good quality information

Dr Simon Day

Aims and Objectives?

- Domenica Taruscio's e-mail to me
- "Our aim is to discuss how robust the evidence of small trials can be in order to better understand how to promote the development of good clinical trials for rare diseases."

“Randomise the first patient”?

- Chalmers TC. When should randomisation begin? *Lancet* 1968: 858.
- Chalmers TC. Randomization of the first patient. *Medical Clinics of North America* 1975; **59**:1035–1038.
- Chalmers TC. Randomize the first patient! *NEJM* 1977; **296**:107.

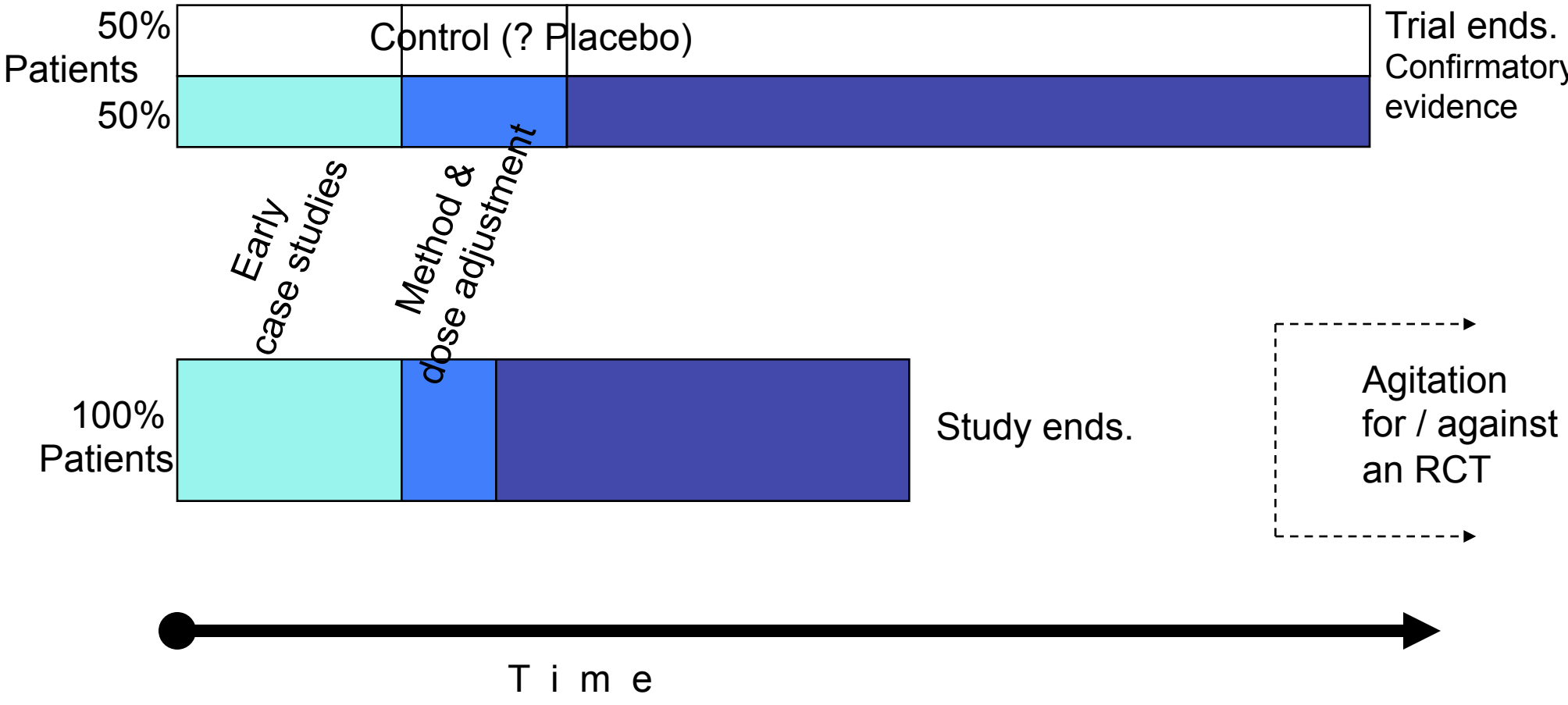
“…some information *vs* good information…”?

- Spodick DH. Randomize the first patient: Scientific, ethical, and behavioral bases. *The American Journal of Cardiology* 1983; **51**:916–917.

- “[it’s always possible to do a randomized trial]… This sacrifices only time (later likely to be more than regained) in the search for a real answer, and ensures an ethical approach that gives every patient a 50–50 chance to get best treatment, that is, not to get the new medicine at a time when its precise effects and risk–benefit ratio are not understood.”

- Data faster: information slower

From Spodick (1983)



Arguments for / against small (efficacy) trials

- 10 patients *vs* 10 patients won't have enough power to show a statistically significant effect
- 10 patients *vs* 0 patients has *zero* power to show a statistically significant effect!
- How can 10 *vs* 10 be worse than 10 vs 0?
- Even 20 patients *vs* 0 patients has zero power

- 1st in man studies (often looking for tolerance) are typically very small
  - They have a tiny chance of showing statistically significant effects (+ve or –ve)
  - But randomisation here seems well accepted

- Might "exposure data" on 20 patients be more useful than "exposure data" on 10 patients (plus 10 controls)
  - Perhaps it might
  - So how about 15 *vs* 5?

When does *more* data give us *less* information?

- Answer: when you have 20 patients on test treatment and no controls
- Whatever effect we see (good or bad), we have no idea “What would have happened if…”

- Similarly, if we have good quality randomised, controlled data pre-licensing (pre-marketing) and then we get (relatively) large amounts of data from use on the market, we *add confusion* and *uncertainty* where before we had clear (even if limited) information
- Maybe when the amount of data grow sufficiently, big numbers overcome lack of control… but only maybe

When does *more* data give us *less* information?

- What about patient registers (registries)?

- Don't get confused between:
  - Historical, controlled trials
  - Historical-controlled trials

- Patient register data *may* help us document the natural course of disease – but we can only document what the natural course of disease *was*, not what it *is*
- Using patient register data as a "control arm" may result in inappropriate (because it's historical), lesser quality (because it's not recorded under such controlled conditions) data

The case for collaboration

- Scientifically, there can be no(?) case against
- An example:
  Penn ZJ, Steer PJ, Grant A. A multicentre randomised controlled trial comparing elective and selective caesarean section for the delivery of preterm breech infant. *British Journal of Obstetrics and Gynaecology* 1996; **103**:684–689.
  - "Intention to deliver vaginally" vs "Intention to deliver by caesarean section"
  - 26 hospitals (all in UK)
  - "Most published data are observational and retrospective and are prone to serious biases. For example […]. The sizes of such biases are likely to be larger than any differential effects of the two methods of delivery."
- Study closed after 17 months; 13 women recruited from 6 hospitals (despite a large potential pool of patients)

The case for collaboration

- Penn ZJ, Steer PJ, Grant A. A multicentre randomised controlled trial comparing elective and selective caesarean section for the delivery of preterm breech infant. *British Journal of Obstetrics and Gynaecology* 1996; **103**:684–689.

- Accompanying editorial:
  Thornton JG, Lilford RJ. Preterm breech babies and randomised trials of rare conditions (commentary). *British Journal of Obstetrics and Gynaecology* 1996; **103**:611–613.
- One of the references is to:
  Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995; **311**:1621–1625.
- And in correspondence following that:
  Brocklehurst P, Elbourne D, Garcia J, McCandlish R. Trials of adequate size are possible with the right organisation (letter). *BMJ* 1995; **311**:1621–1625.
  "…A trial of the management of posthaemorrhagic ventricular dilatation in neonates is currently recruiting from 137 centres in 26 countries…."