Does industry involvement influence study characteristics at time of trial registration?

Anna Lene Seidler, Kylie Hunter, Lisa Askie

Australian New Zealand Clinical Trials Registry (ANZCTR)
NHMRC Clinical Trials Centre
University of Sydney, Australia

Background

A large proportion of clinical trials funded or conducted by industry

- e.g. 70% of money for drug trials in the US comes from the industry (Bodenheimer, 2000)

Industry bias: industry-sponsored trials show higher efficacy and less harm (Lundh, 2011)

- Favourable efficacy results (RR 1.32, 95% CI 1.21 to 1.44)
- Favourable harm results (RR 1.87, 95% CI 1.54 to 2.27)

Differences persist even when controlling for methodological biases

- e.g. no difference on Cochrane risk of bias tool

What are the mechanisms that lead to more favourable results in industry trials?

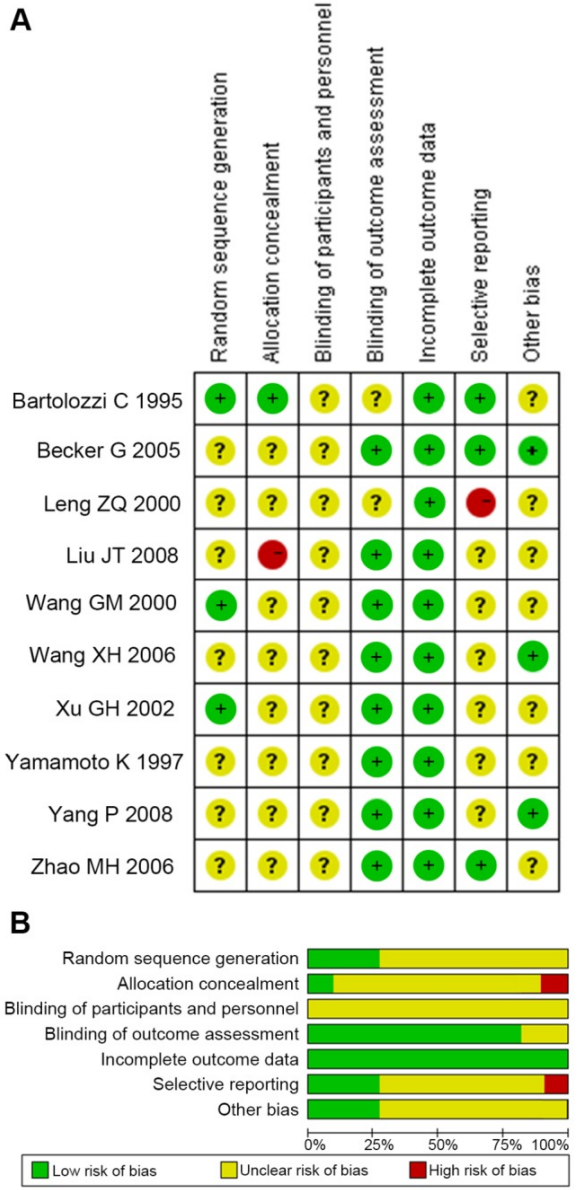
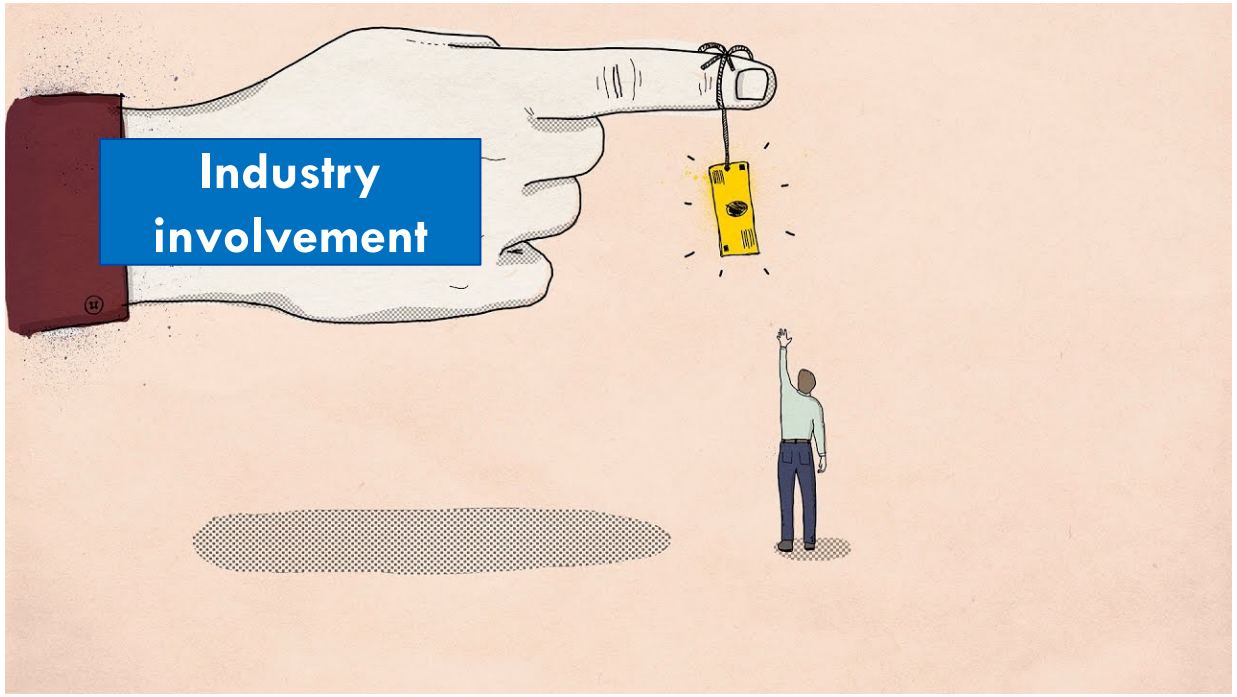


Figure. Example of Cochrane risk of bias assessment

Objective

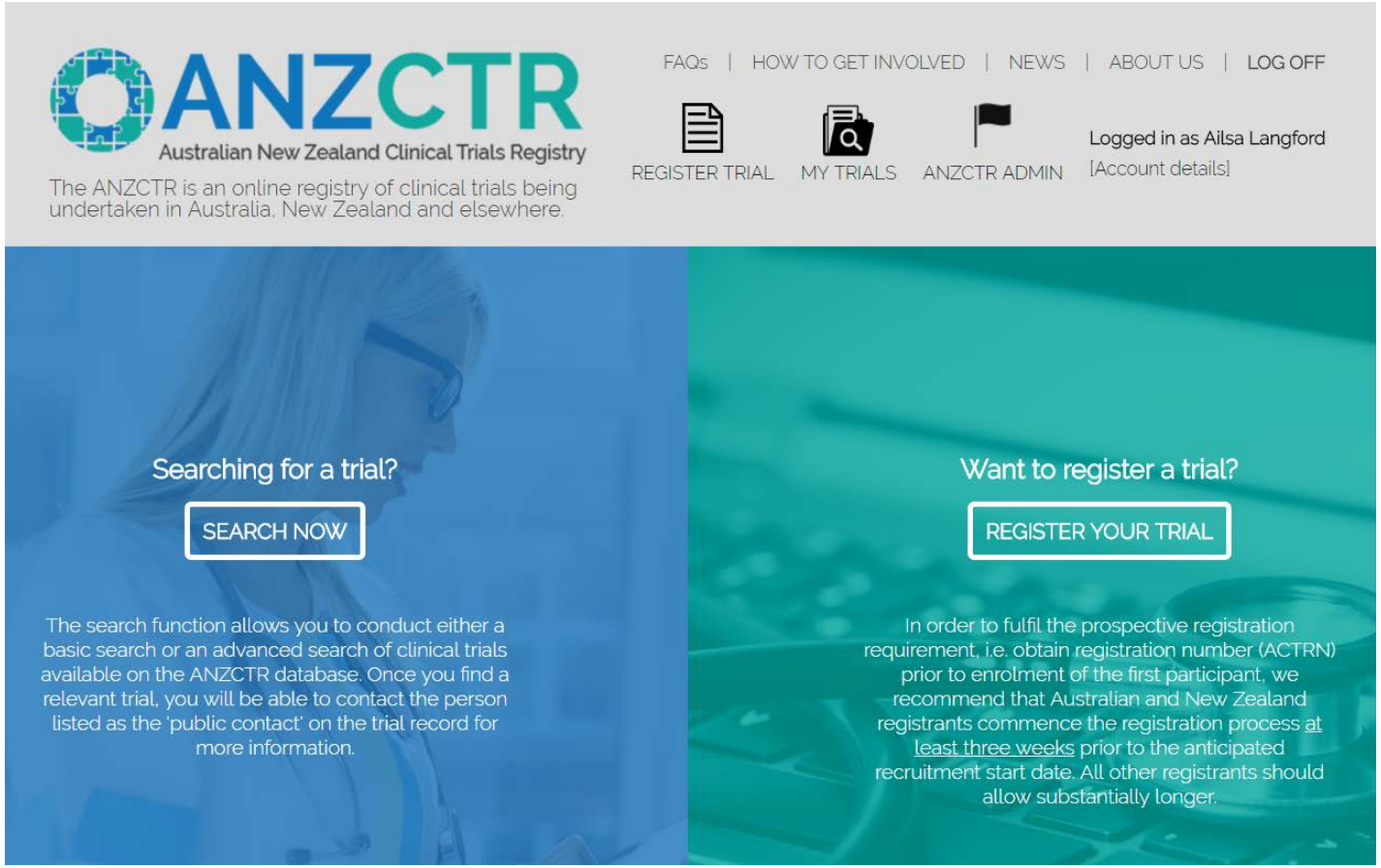
To determine whether industry involvement is associated with trial characteristics at the time of trial registration



Trial characteristics

Methods

- Included all 1,433 interventional studies registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) in 2017
- ANZCTR recognised by World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry
- Trials from all over the world, but most trials (almost 90%) Australian or New Zealand trials



www.anzctr.org.au

Methods - measures

Industry (i.e. commercial sector)

Any industry involvement (any industry funding, sponsorship or collaboration)

Funding financial/material/infrastructure support for the study

Primary sponsor individual/organisation initiating and managing the study, usually the principal investigator

Collaborator individuals/organisations that have also agreed to take on responsibilities of sponsorship

Primary sponsor type (e.g. industry, university, hospital, government, charities)

Trial characteristics

Type of control active, placebo, no treatment, uncontrolled

Sample size number of participants per trial

Study phase phase 1, phase 2, phase 3, phase 4

Randomised allocation randomised-controlled trial versus non-randomised trial

Registration timing prospective registration (i.e. before enrolment of first participant) versus retrospective

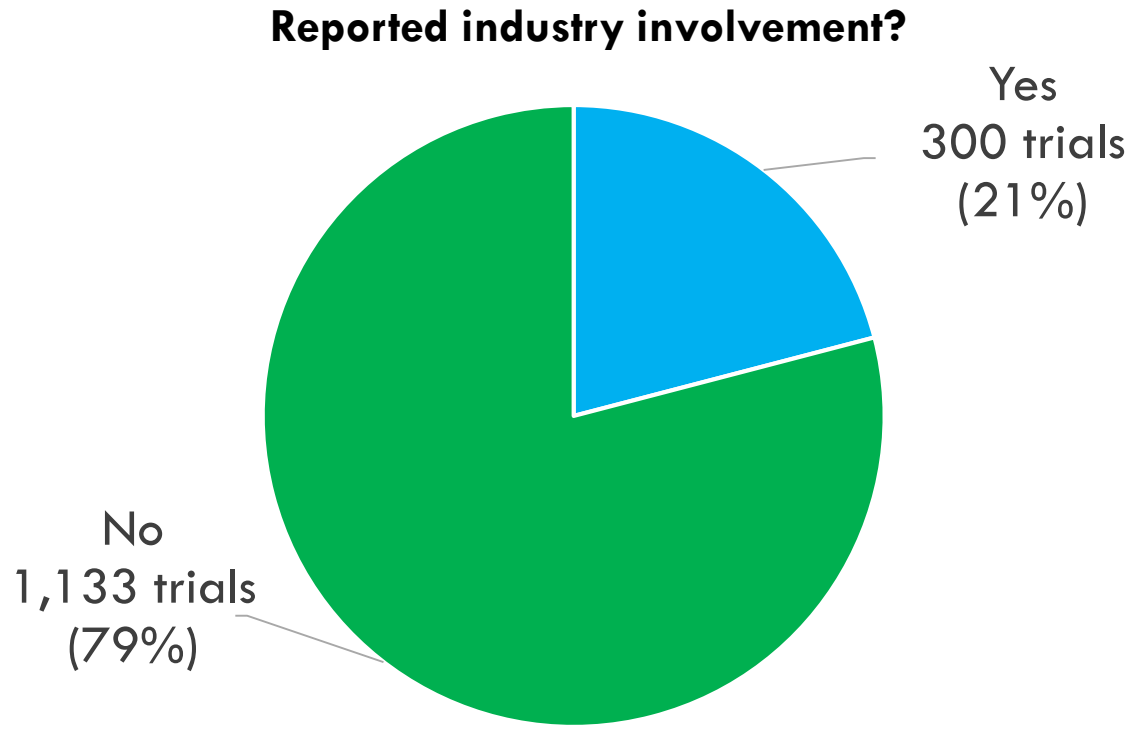
Study purpose treatment, prevention, diagnosis or education

Methods - analysis

- Descriptive analysis: numbers and proportions
- Odds ratios (OR)
- Mean difference
- Chi-square tests

Results - landscape of industry funding for trials on ANZCTR in 2017

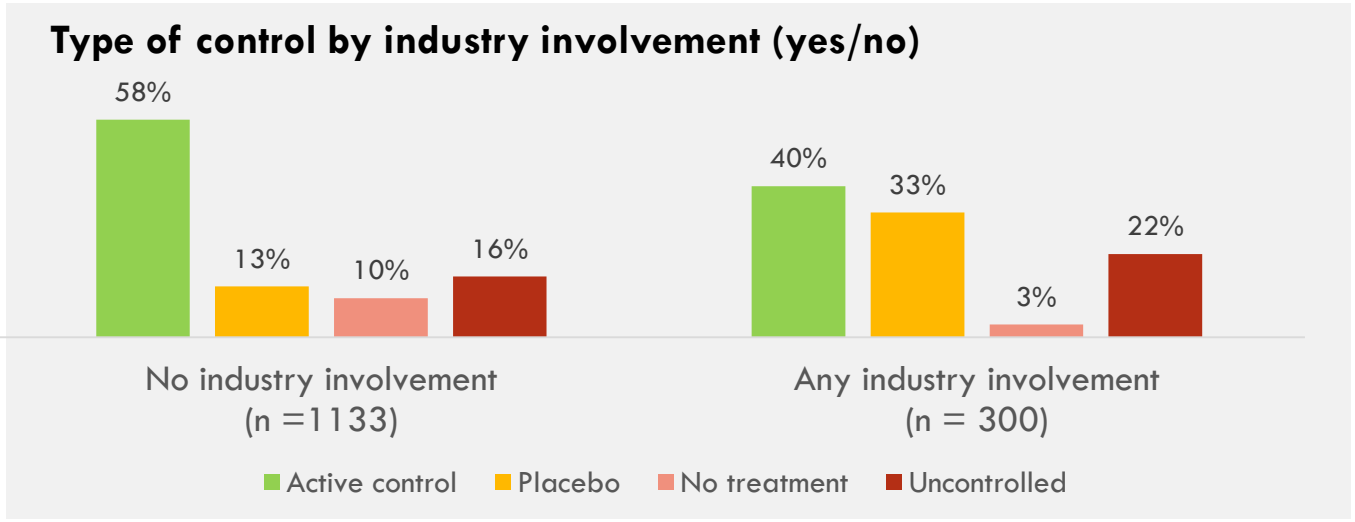
- 1,433 included trials
- 300 (21%) reported some kind of involvement from the commercial sector (industry funding, sponsor or collaborator)
  - 285 (95%) of these reported funding by the industry
  - 153 (51%) of these had a primary industry sponsor
  - 12 (4%) of these had an industry collaborator

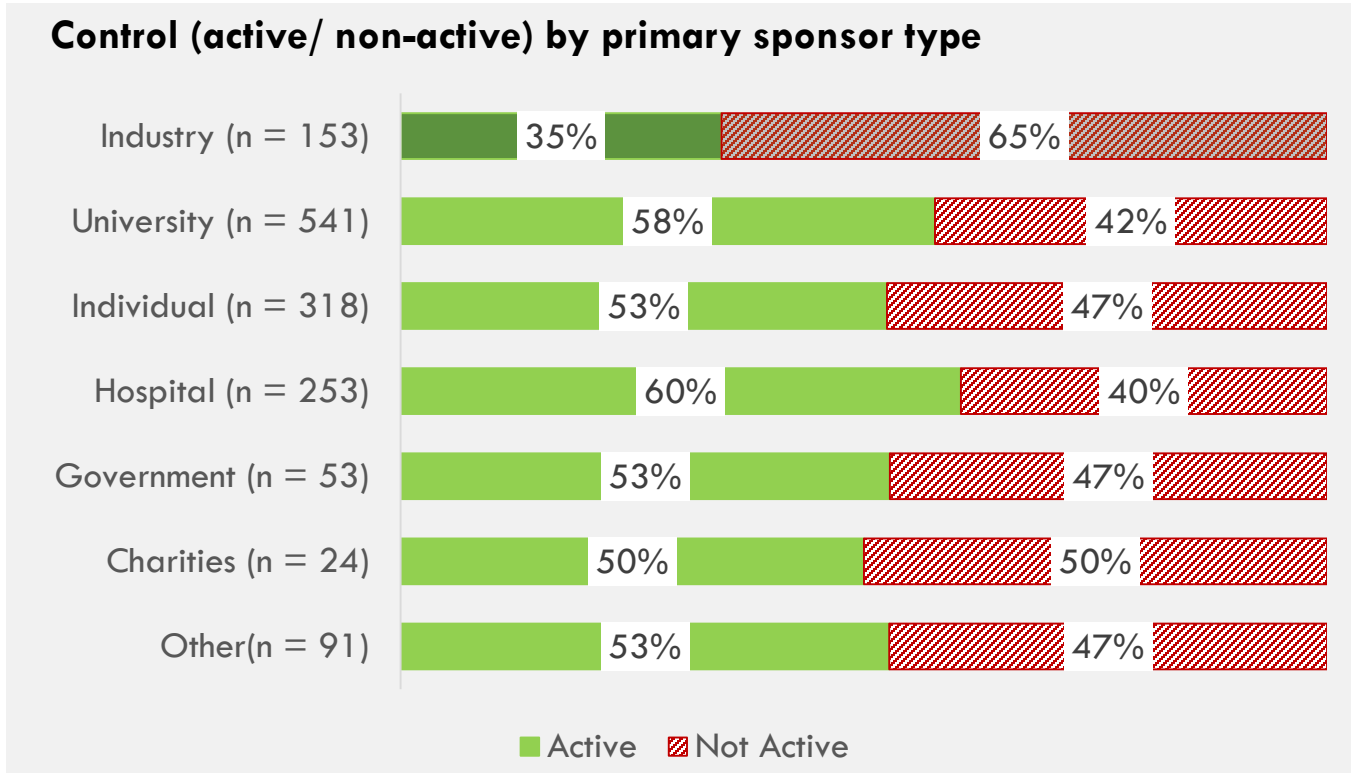


Type of control

Trials with industry involvement **less likely to use active controls**
OR = 0.49, 95% CI = 0.38-0.63

This effect is even more pronounced when looking at **industry sponsorship**
(i.e. study conducted by industry)
OR = 0.39, 95% CI = 0.27-0.56
Reference group: university sponsor (largest group)



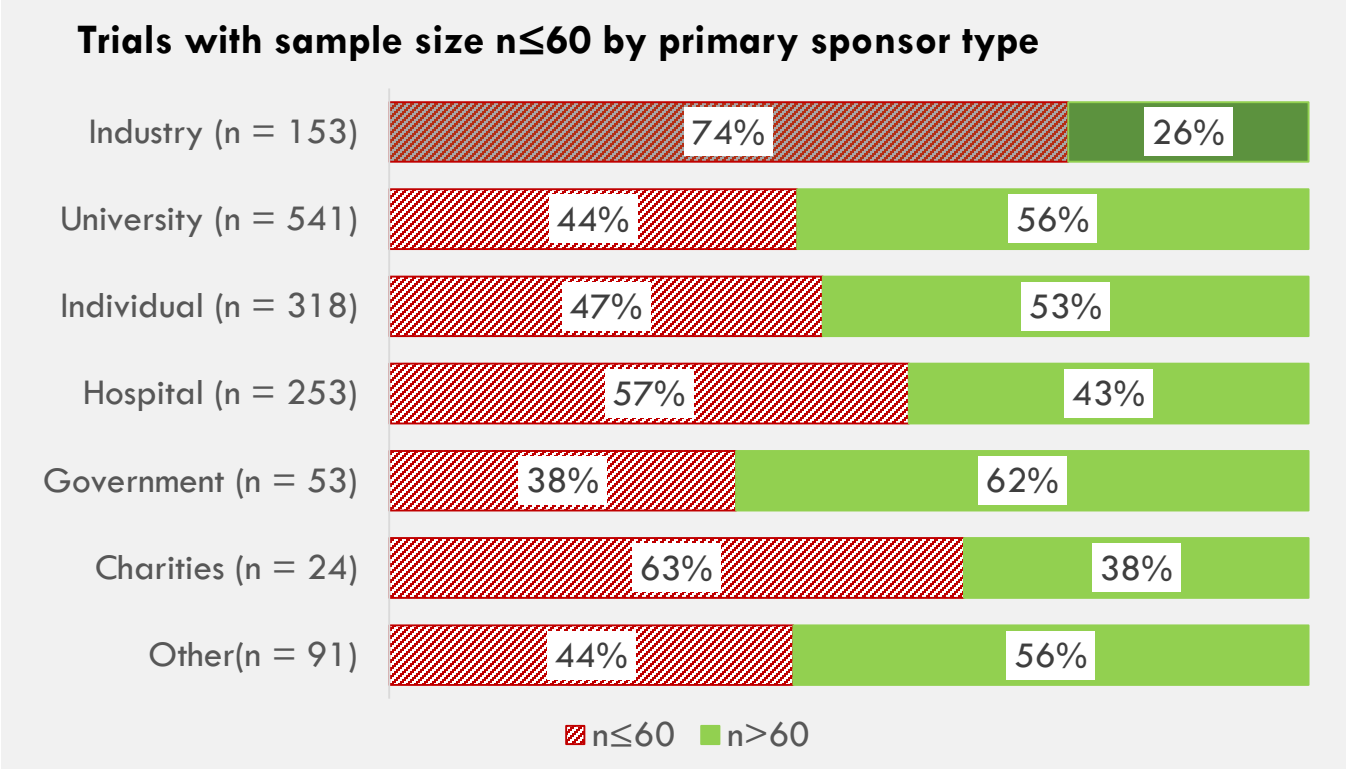


Sample size

Trials with industry involvement are **smaller on average**
MD = -153.00
95% CI -231.99 to -73.90

Trials with industry sponsorship are **more likely to have a sample size below 60** (Median)
OR = 0.28, 95% CI 0.19 to 0.42

Sample size	Sample size Median (IQR)	Sample size Mean (SD)
No industry involvement (n = 1,133)	70 (125)	249 (689)
Any industry involvement (n = 300)	45 (76)	96 (198)



Industry involvement and phase

- Significant difference between trials with and without industry funding by trial phase $X^2(4) = 71.46$, $p < .0001$
- Trials with industry involvement more likely to be early trials
- Trials without industry involvement more likely to be post-marketing trials

Limitation: phase data only available for **364 (25%)** out of 1,433 trials

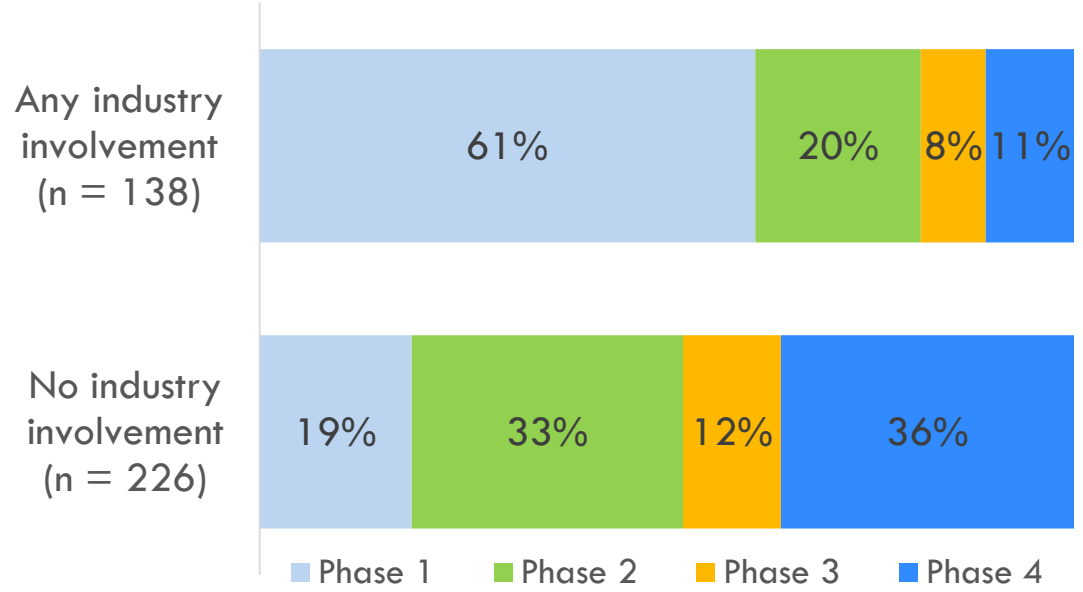
Trial phases

Phase 1: evaluate metabolism and pharmacological action of drugs, and monitor side effects.

Phase 2: evaluate the effectiveness of new drugs in patients with the disease or condition being studied and to determine common short-term side effects and risks

Phase 3: additional information on benefits and risk, including possible adverse reactions

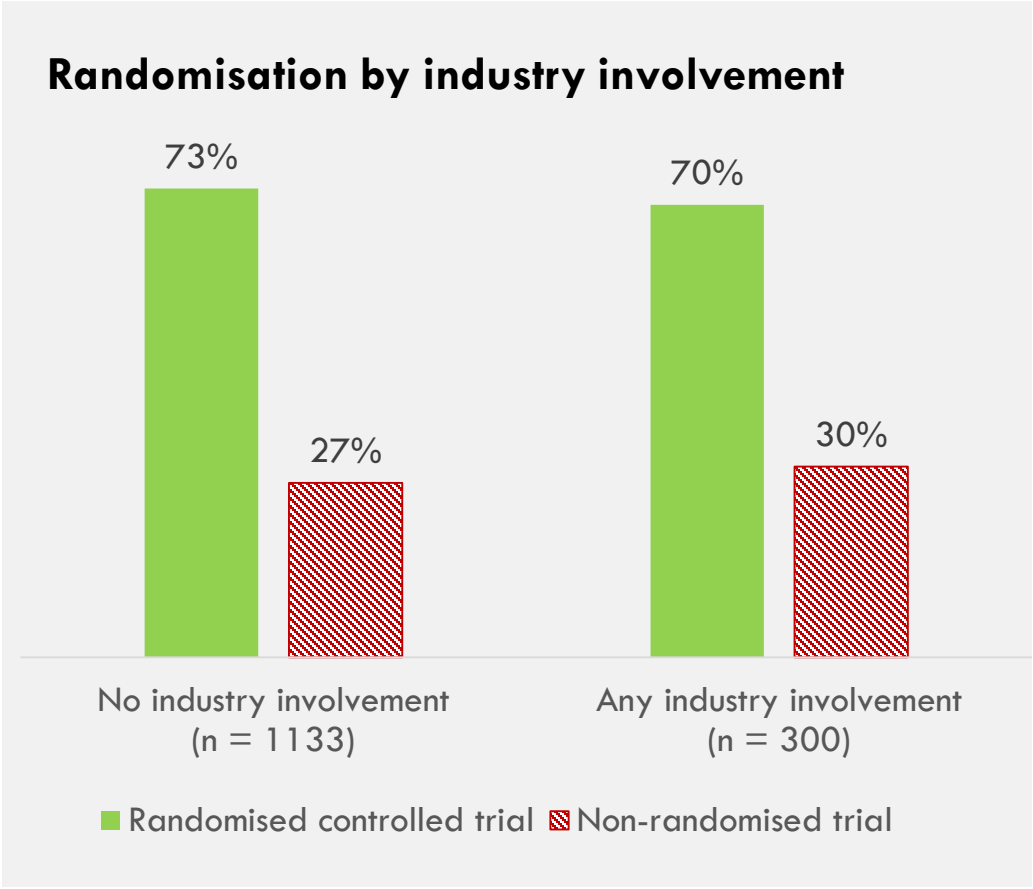
Phase 4: additional information after a drug has been marketed, monitoring aspects such as toxicity, risks, utility, benefits and optimal use



Randomisation

No significant difference between industry and non-industry trials in randomisation

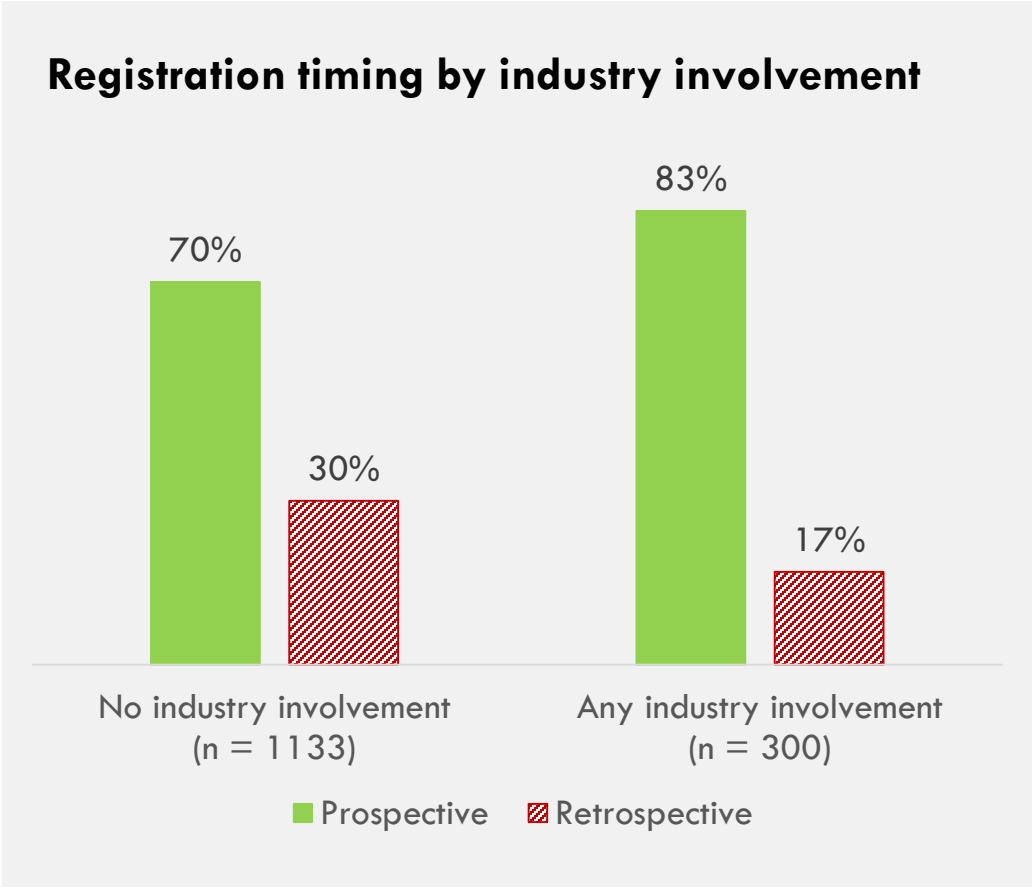
OR = 0.88, 95% CI 0.67 to 1.20



Prospective registration

Industry trials **more likely to be prospectively registered** (i.e. registered on ANZCTR before enrolment of the first participant)

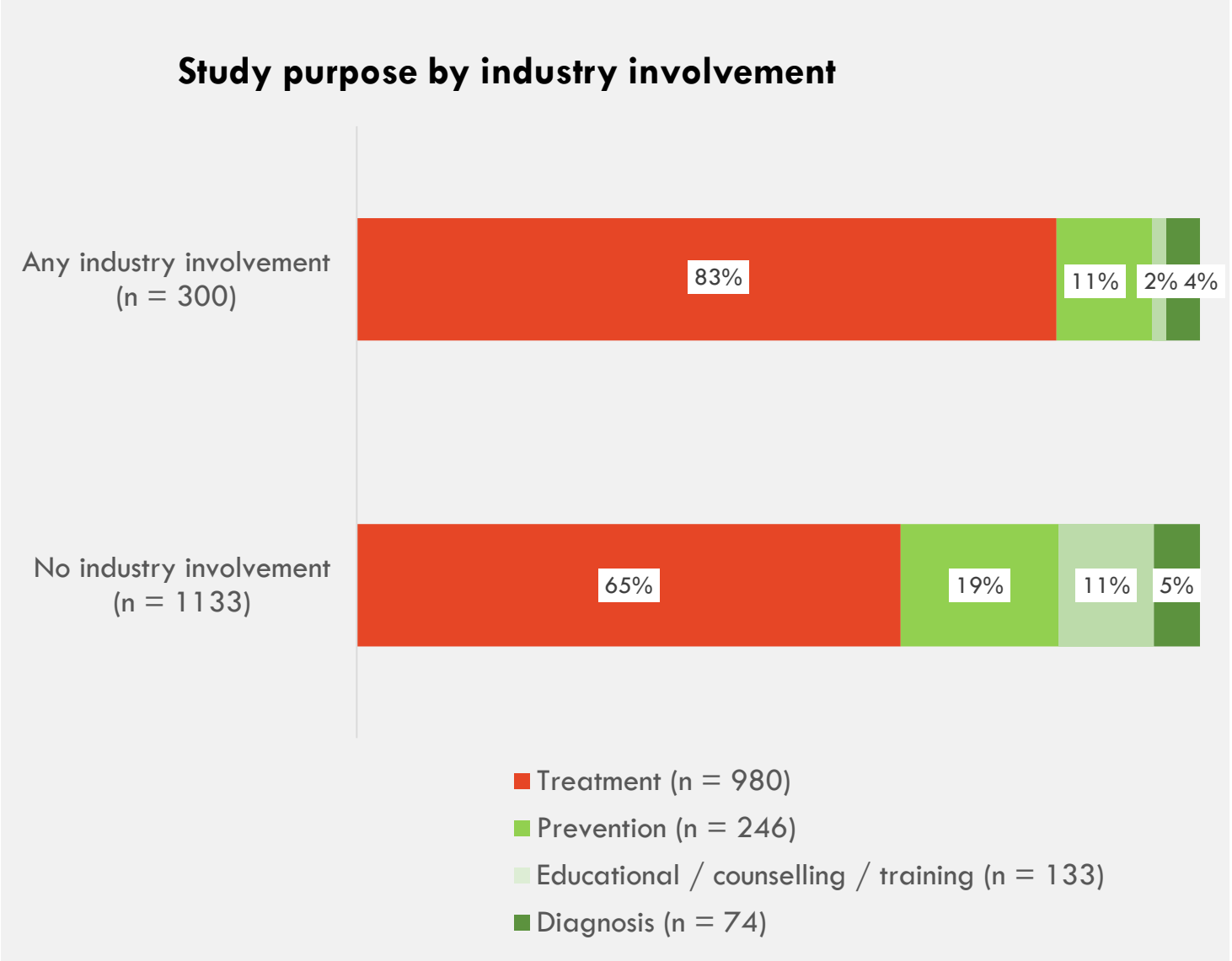
OR = 2.02, 95% CI 1.47 to 2.82



Purpose of study

Trials with industry involvement are more likely be aimed at treatment
OR = 2.68
95% CI = 1.95 to 3.75

Industry trials less likely to list prevention, education or diagnosis as their primary purpose



Summary of findings and implications

Industry trials less likely to use an active control

Placebo and no-treatment controls likely to yield more favourable effects

Industry trials smaller on average

Smaller trials tend to exaggerate effects

Industry trials more likely to be earlier phase trials

This may explain some of the observed differences (but only known for 25% of trials)

Industry trials equally likely to use random allocation

A domain usually applied for assessing risk of bias

Industry trials more likely to be prospectively registered

A domain usually applied for assessing risk of bias

Industry trials more likely to be aimed at treatment

Other funding sources necessary to ensure trials on prevention, education and diagnosis

Limitations

- These are exploratory, correlational analyses!
- Differences may partly be explained by different study types
  - Industry-funded trials more likely to be early phase trials
  - For some treatments there is no current gold standard and placebo is the best comparison
- ANZCTR data may not be representative of all trials
  - Previous studies find higher proportions of industry funding than the current study
  - Other trial registries (e.g. Clinical Trials.gov) register a higher proportion of industry-funded trials

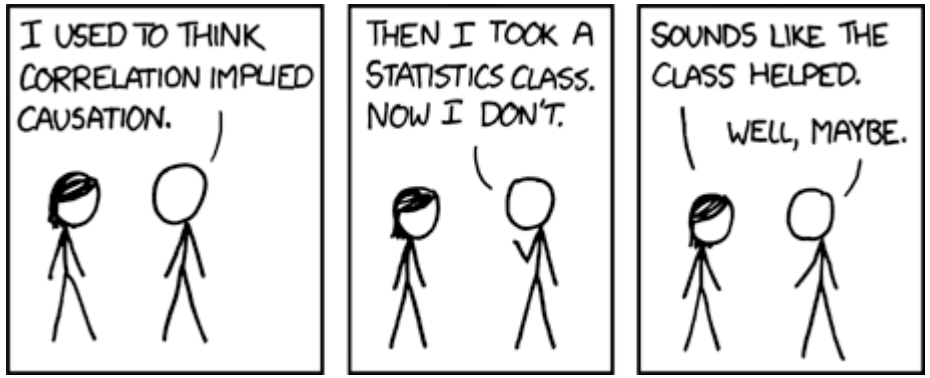
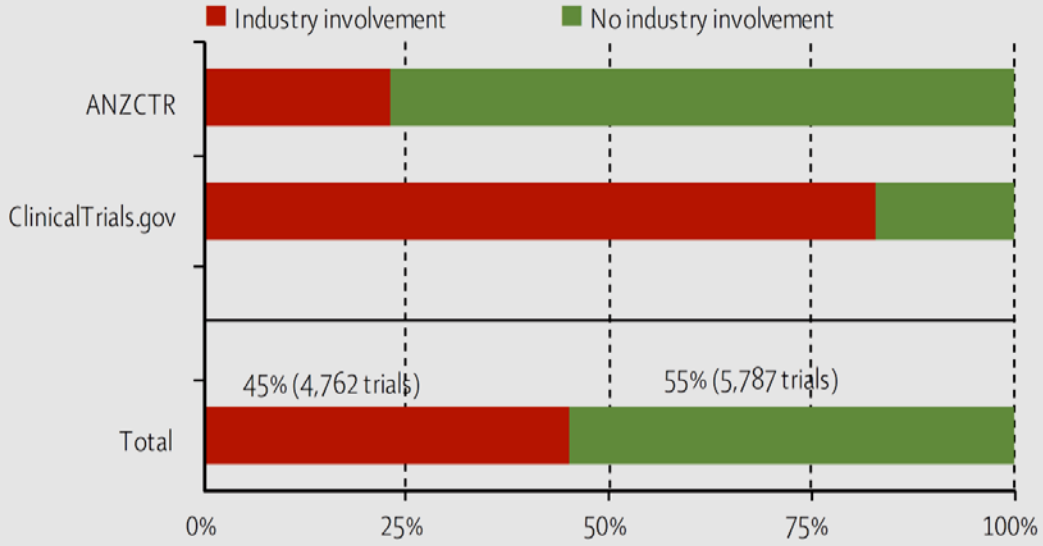


Figure 9. Proportion of Australian clinical trials registered 2006–2015 with any industry involvement



Askie et al, 2017

Conclusions

1. Less active controls & smaller sample sizes are potential mechanisms creating industry bias (but be aware of limitations!)

2. Industry bias not evident in 'traditional' risk of bias assessment domains (randomisation and prospective registration)

3. Non-industry research crucial to ensure research addresses not only treatment, but also prevention and education questions

Thank you!

lene.seidler@ctc.usyd.edu.au
@LeneSeidler

References

1. Lundh A, Sismondo S, Lexchin J, Busuioc O, Bero L: **Industry sponsorship and research outcome.** *The Cochrane database of systematic reviews* 2011, **12**.
2. Bodenheimer T: **Uneasy Alliance — Clinical Investigators and the Pharmaceutical Industry.** *NEJM* 2000, **342**(20):1539-1544.
3. Askie LM, Hunter KE, Berber S, Langford A, Tan-Koay AG, Vu T, Sausa R, Seidler AL, Ko H, Simes RJ. The clinical trials landscape in Australia 2006–2015. Sydney: Australian New Zealand Clinical Trials Registry 2017.
4. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials. gov. Annals of Internal Medicine. 2010 Aug 3;153(3):158-66.