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Resources for authors and journals

The problem of publication bias and waste in research

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Themes

- Why does research waste matter?
- When / how does waste occur?
- What harm does research waste do?
- How can we reduce waste in research?

For more details see Lancet series:
http://www.thelancet.com/series/research

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Research funding is finite

If someone takes a slice there is less left for everybody else …

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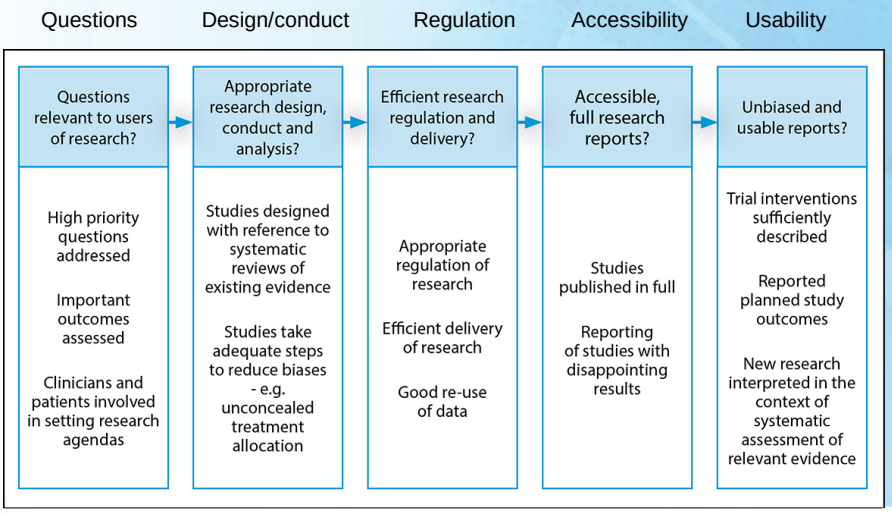
Waste occurs in all stages of research



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Ethical impacts

1. Asking the wrong questions
2. Weak study designs
3. Not publishing all research
4. Poor reporting quality

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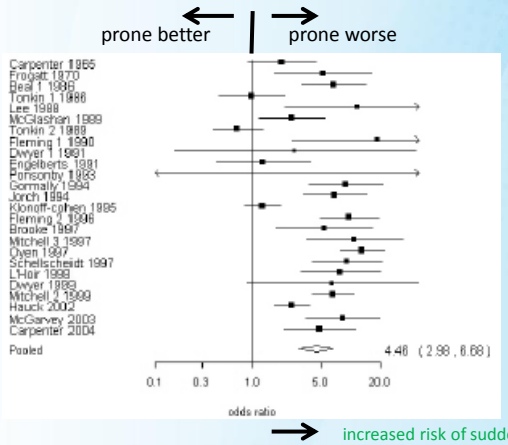
Sleeping position and sudden infant death



Individual studies (by year) 1965-2004

Gilbert et al *Int J Epidemiol* 2005;**34:**874

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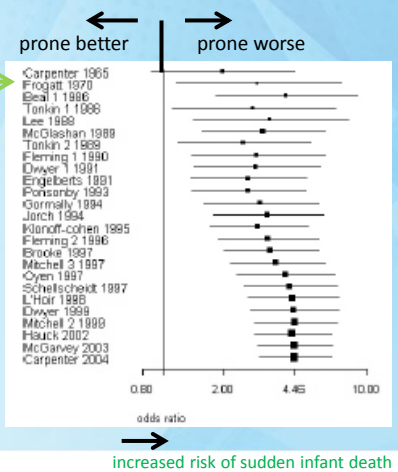
Sleeping position and sudden infant death

Cumulative effect (by year)

Clear effect by 1970



Gilbert et al *Int J Epidemiol* 2005;**34:**874

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This mother was right!

- Up to 1988 UK & US books recommended babies should sleep on their front
- But since 1970 there was clear evidence that front sleeping significantly **increased** sudden infant death
- Earlier recognition of risk of front sleeping could have prevented >60,000 infant deaths

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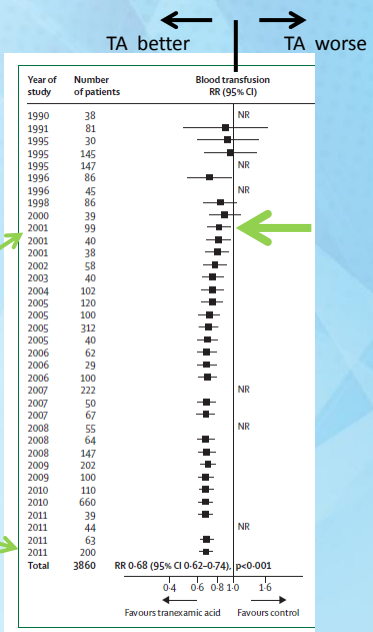
Effect of tranexamic acid on blood loss during surgery

Cumulative meta-analysis shows effect by 2001 but trials continue until 2011



Based on Ker et al *BMJ* 2012;**344**:e3054

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Asking the wrong question

- Patients undergoing surgery involved in unnecessary trials, some receiving sub-optimal treatment, despite clear evidence that tranexamic acid reduces blood loss
- BUT, despite all the studies, they were too small to show whether tranexamic acid also reduced heart attacks and death

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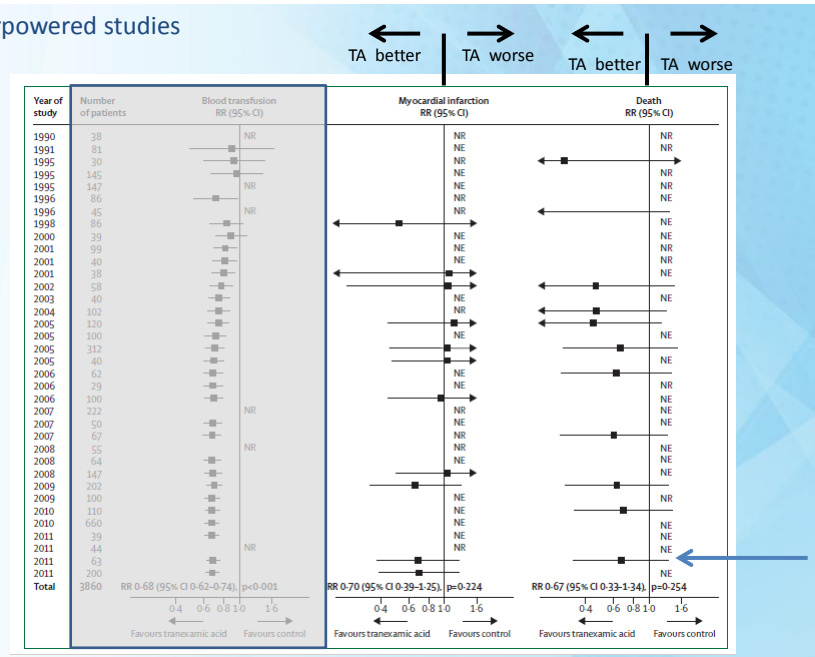
Underpowered studies



Heart attack Death

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Underpowered studies

- Big problem in preclinical (animal) research
- Risk of not detecting true effect and reporting 'false positive' effect

- Systematic reviews found:
  3% studies in stroke
  0% in Alzheimer's / Parkinson's disease
  reported sample size calculation

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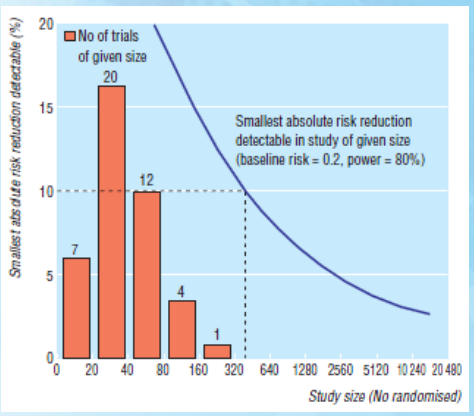
Underpowered studies

- Meta-analysis of 44 animal studies of fluid resuscitation
- Average number of animals / treatment group was 13
- No trial was large enough to reliably detect a 10% absolute difference (halving) in risk of death



Trial size and smallest absolute risk reduction detectable

Roberts et al *BMJ* 2002;**324**:474

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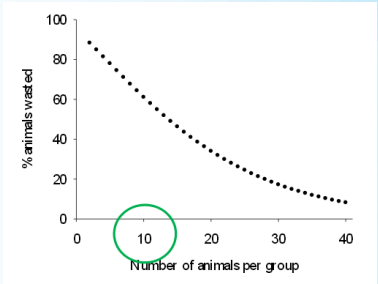
Wasting lab animals

Number of animals	Power	% animals wasted
4	18.6%	81.4%
8	32.3%	67.7%
16	56.4%	43.6%
32	85.1%	14.9%



Chances of wasting an animal in 2-group study seeking 30% reduction in infarct volume with SD = 40%

From CAMARADES

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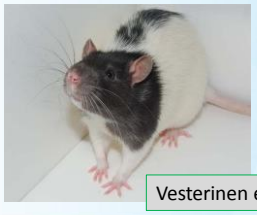
Poor design in animal studies on multiple sclerosis

- Meta-analysis of 1117 publications
  - 9% reported random allocation to group
  - 16% had blinded assessment of outcome
  - <1% had sample size calculation



Vesterinen et al *MS* 2010;**16:**1044

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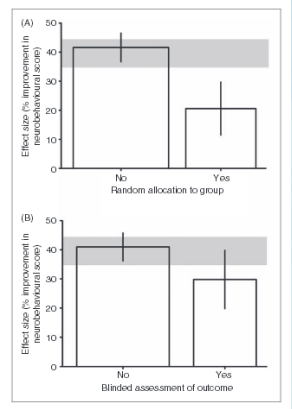
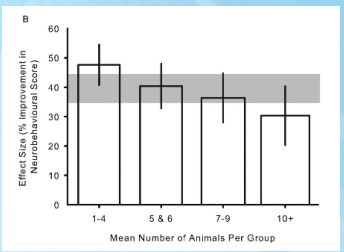
Weak design in animal studies over-estimates effect size

Randomization

Blinded assessment





Group size

Review of 1117 studies in multiple sclerosis

Vesterinen et al *MS* 2010;**16:**1044

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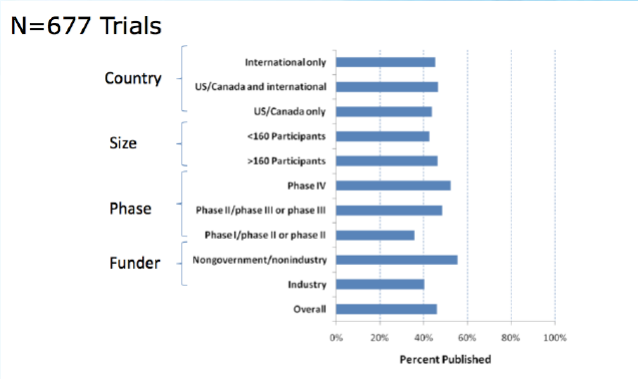
Half of all clinical trials are never published



Ross et al *PLOS Med* 2009;e1000144

Publication rate may be higher for more recent studies but publication bias affects the literature on most prescribed medicines

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Evidence of non-publication of large trials

- 585 registered trials with >500 participants
- Completed before Jan 2009
- 29% (171) unpublished in November 2012
- Of the unpublished trials 78% did not have results posted on CT.gov
- *"The lack of availability of results from these trials … constitutes **a failure to honour the ethical contract** that is the basis for exposing study participants to the risks inherent in trial participation. Additional safeguards are needed to ensure timely public dissemination of trial data."*

Jones et al *BMJ* 2013;**347**:f6104

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The scale of publication bias

- About 50% of studies presented at conferences never get published in full
  (Scherer et al *JAMA* 1994;**272**:158-62)
- Cohort of RCTs submitted to Swiss REC (to 1998) 52% published by 2006
  (von Elm et al *Swiss Med Wkly* 2008;**138**:197-203)
- 22% of trials on CT.gov reported results within 1 year of study end
  (Prayle et al *BMJ* 2012)

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50% of clinical trials unpublished

Of EU-funded health research 1998-2006

- 50% unpublished
- 570 million Euros of research had "no detectable academic output"

Galsworthy et al *Lancet* 2012;**380**:971

- Situation may be improving but evidence-base for most prescribed medicines is badly affected by non-publication

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Effects of publication bias

- German drug assessment body found 74% of data on the antidepressant reboxitine was unpublished
- Including the unpublished data changed their recommendation (to "ineffective and potentially harmful")

Wieseler et al *BMJ* 2010;**341**:c4942
Eyding et al *BMJ* 2010;**341**:c4737

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Why does publication bias matter?

- Clinical decisions are based on medical evidence
- If the evidence-base is distorted, the decisions may not be correct
- Guidelines are often based on systematic reviews / meta-analyses – these can be distorted by publication bias

- Publication bias is a major problem
- It is caused by:
  - Non-publication of trials with negative findings
  - Selective publication of positive outcomes
  - (Redundant publication of positive trials)
- It can be reduced by:
  - Trial registration
  - Publishing protocols
  - Rewarding researchers / companies for responsible publication (?punishing non-publication)

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Much published research is unusable

- Of 102 journal articles reporting clinical trials, 62% had a change to the primary outcome stated in the protocol
- Of 88 studies using novel questionnaires only 8% of questionnaire could be accessed
- Of 141 studies of test accuracy, 40% did not report participants' age and sex
- Of 49 AIDS trials, only 33% reported all adverse events

All refs in Glasziou et al *Lancet*, 2014

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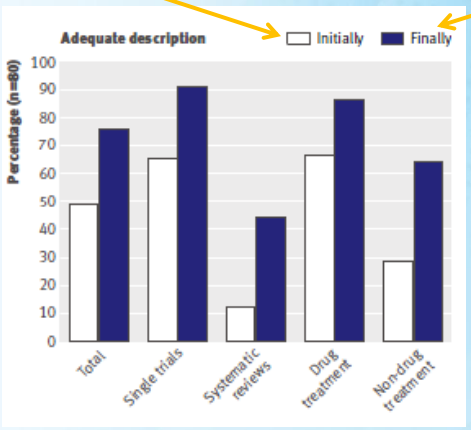
Inadequate treatment descriptions in 80 studies of medical therapies from journal article and supplementary info



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Glasziou et al *BMJ*, 2008;**336**:1472

Conclusions

- Waste in research is a major problem
- Waste is an ethical issue because:
  - research resources are finite
  - patients / volunteers / animals take part in unnecessary studies
  - decisions (affecting patient treatments, public policies) are based on flawed evidence-base (incomplete, biased, misleading reporting)
- Publication bias (selective reporting / non-publication) is a major cause of research waste

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How can we reduce waste in research?

- Demand justification of study question
- Support research synthesis so it's clear what is already known
- Enforce trial / study registration
- Use strong designs that maximize the effect-to-bias ratio
- Reward reproducible research
- Reward full and effective dissemination of findings (and re-use of datasets)
- Support use of reporting guidelines

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Initiatives to reduce waste in medical research

- Prioritisation / question setting
- Trial registration
- Full reporting
- High quality reporting

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REduce research WAste and Reward Diligence

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Questions

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