



Why is waste in research an ethical issue?

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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?

Weak designs

Wrong questions

Publication bias

Unusable reports

THE LANCET

"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

arch: increasing value, reducing waste

Research funding is finite



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

Waste occurs in all stages of research

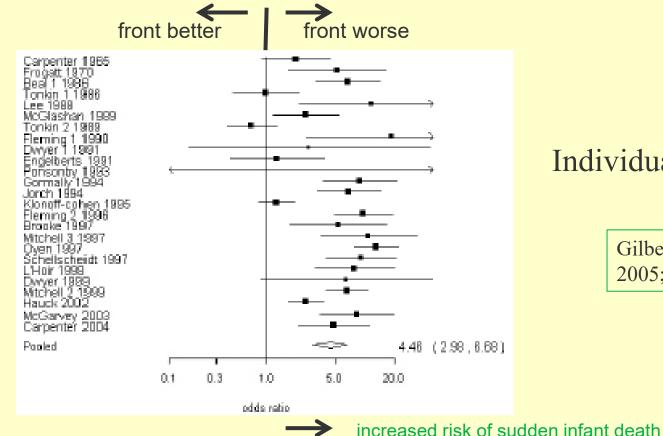
Questions	Design/conduct	Regulation	Accessibility	Usability
Questions relevant to users of research?	Appropriate research design, conduct and analysis?	Efficient research regulation and delivery?	Accessible, full research reports?	Unbiased and usable reports?
High priority questions addressed Important outcomes assessed Clinicians and patients involved in setting research agendas	Studies designed with reference to systematic reviews of existing evidence Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation	Appropriate regulation of research Efficient delivery of research Good re-use of data	Studies published in full Reporting of studies with disappointing results	Trial interventions sufficiently described Reported planned study outcomes New research interpreted in the context of systematic assessment of relevant evidence

Ethical impacts

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



Sleeping position and sudden infant death



Individual studies (by year) 1965-2004

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

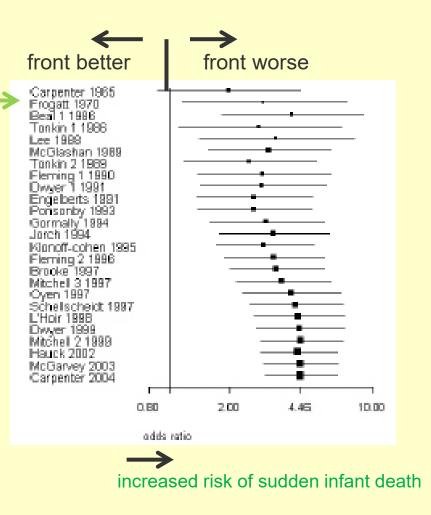
Wrong questions



Sleeping position and sudden infant death

Cumulative effect (by year) Clear effect by 1970-

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



Wrong questions



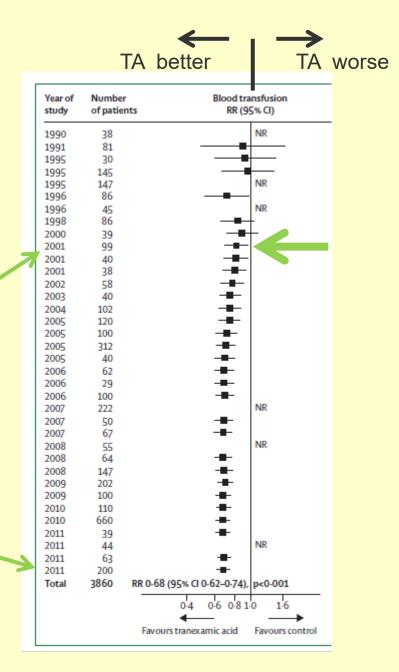
This mother was right!

- 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

Effect of tranexamic acid (TA) on blood loss during surgery

Cumulative metaanalysis shows effect by 2001 but trials continue until 2011

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

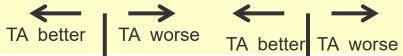


Wrong questions

Asking the wrong question Weak study design

- Patients undergoing surgery involved in unnecessary trials, some receiving suboptimal 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

Underpowered studies



Death

	Number of patients	Blood transfusion RR (95% CI)	Myocardial infarction RR (95% CI)	Death RR (95% CI)
90	38	NR	NR	NR
91	81		NE	NR
95	30		NR	← ■ →
95	145		NE	NR
95	147	NR	NE	NR
96	86		NR	NE
96	45	NR	NR	←
98	86			NE
00	39		NE	NE
01	99		NE	NR
01	40		NE	NR
01	38			NE
02	58		→	← ■
03	40		NE	NE
04	102		NR	← ■
05	120			← ■ ───────────────
05	100		NE	NE
05	312			
05	40			NE
06	62		NE	
06	29		NE	NR
06	100			NE
07	222	NR	NR	NE
07	50		NE	NE
007	67		NR	
800	55	NR	NR	NE
800	64		NE	NE
800	147			NE
09	202	*	NE	
09	100			NR
10	110		NE	
	660	-	NE	NE
11	39	- NR	NR	NE
11	44		INK	NE
11	63	*		NE
)11	200		00.070/05** (10.20.4.25) = 0.224	
otal 3	3860 RR 0-68	3 (95% CI 0-62-0-74), p<0-001	RR 0.70 (95% CI 0.39–1.25), p=0.224	RR 0-67 (95% CI 0-33-1-34), p=0-254
		0.4 0.6 0.8 1.0 1.6	0.4 0.6 0.8 1.0 1.6	0.4 0.6 0.8 1.0 1.6
	Favor	urs tranexamic acid Favours cont	Favours tranexamic acid Favours control	Favours tranexamic acid Favours control
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Heart attack

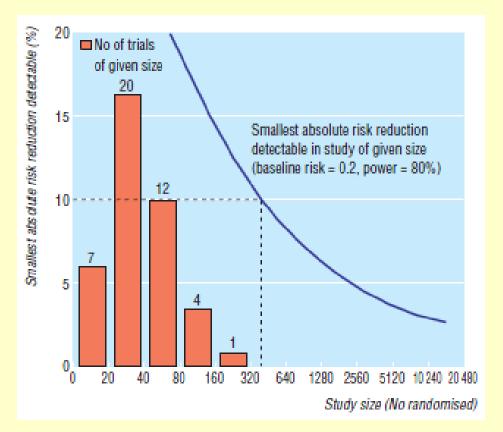
Underpowered studies

- Big problem in preclinical (animal) research
- Risk of not detecting true effect <u>and</u> reporting 'false positive' effect
- Systematic reviews found: 3% animal studies in stroke 0% in Alzheimer's / Parkinson's disease reported sample size calculation

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

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

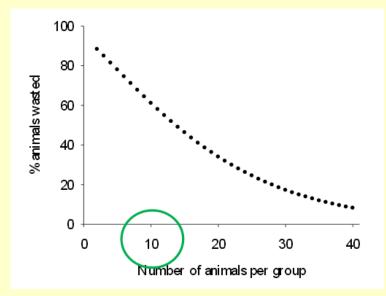


Trial size and smallest absolute risk reduction detectable



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

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

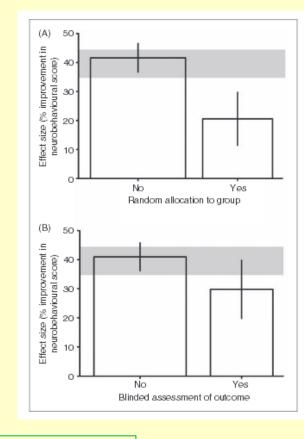


Weak design in animal studies over-estimates effect size

Randomization

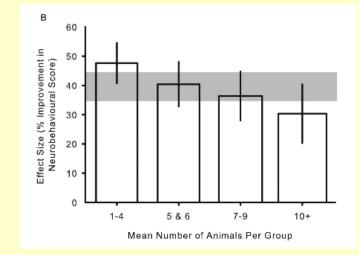
Blinded

assessment



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

Weak designs



Group size

Review of 1117 studies in multiple sclerosis

Much research is never published

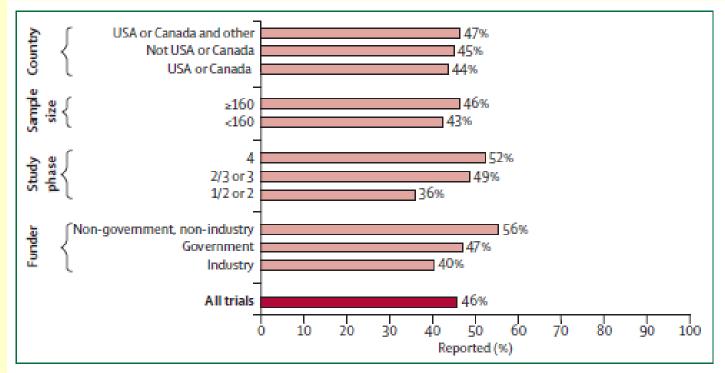


Figure 2: Reporting of completed trials, by study characteristic

Data taken from Ross and colleagues' analysis¹¹ of a random sample of 677 completed trials registered with ClinicalTrials.gov between 2000 and 2007.

Publication bias

50% of clinical trials unpublished

Of EU-funded health research 1998-2006

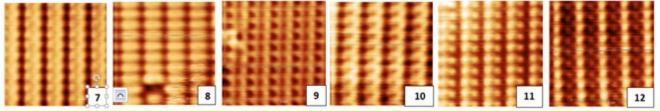
50% unpublished

Galsworthy et al Lancet 2012;380:971

- 570 million Euros of research had
 "no detectable academic output"
- Situation may be improving but evidencebase for most prescribed medicines is badly affected by non-publication

Non-publication of negative studies also a problem in physics

- Scanning probe microscopy (SPM) uses a 'single atom tip' to map structures
- Many SPM images are discarded because they don't show the "correct" image (because the tip isn't in the right state)



Effect of tip state on images (same sample and conditions) Acknowledgement: Philip Moriarty / Morten Moller, Univ Nottingham

How do researchers decide on what the "correct" image is?
Publication bias

Publication bias affects the social sciences

- 221 social science experiments (NSF funded, rigorous quality review)
- Strong results 40% more likely to be published than null results
- 60% more likely to be written up at all
- Authors concluded: "Authors do not write up and submit null findings"

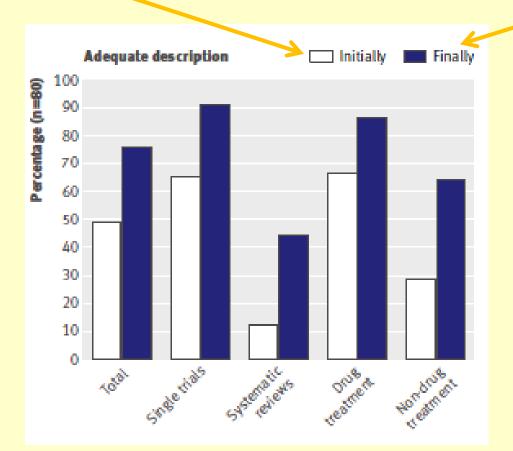
Franco et al *Science* 2014;**345**:1502

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

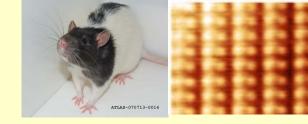
Inadequate treatment descriptions in 80 studies of medical therapies from journal article and supplementary info



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

Unusable reports





Conclusions

- Waste in research is a major problem
- Waste affects many disciplines
- 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)

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



By ensuing that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

Research: increasing value, reducing wast

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Initiatives to reduce waste in medical research

- Prioritisation / question setting James Lind Alliance
- Trial registration ClinicalTrials.gov
- Full reporting
- High quality reporting







<u>**RE</u>**duce research <u>**WA**</u>ste and <u>**R**</u>eward <u>**D**</u>iligence</u>

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PROSPERO

Links





REduce research WAste and Reward Diligence

http://researchwaste.net/



Enhancing the QUA lity and Transparency Of health Research www.equator-network.org/

REWARD / EQUATOR conference on research waste Edinburgh, UK, 28-30th Sept, 2015

http://researchwaste.net/research-wasteequator-conference/

THE LANCET

Research: increasing value, reducing waste

http://www.thelancet.com/series/research

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