Women's College Hospital

Transparency: An imperative in clinical research

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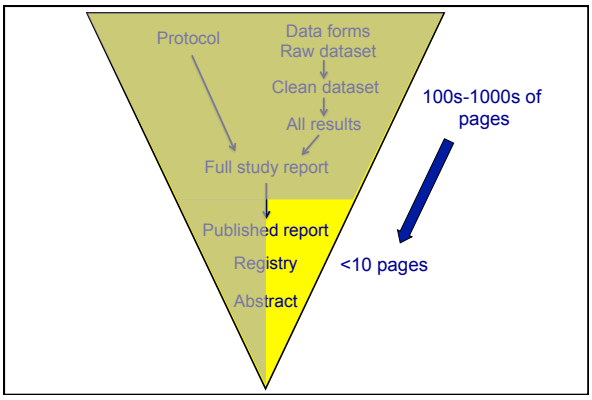
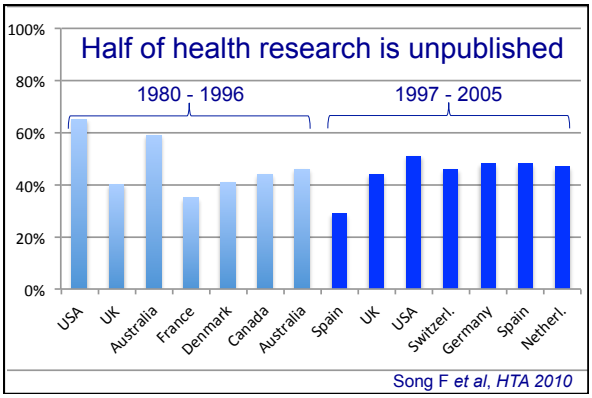
Landscape of randomized trials

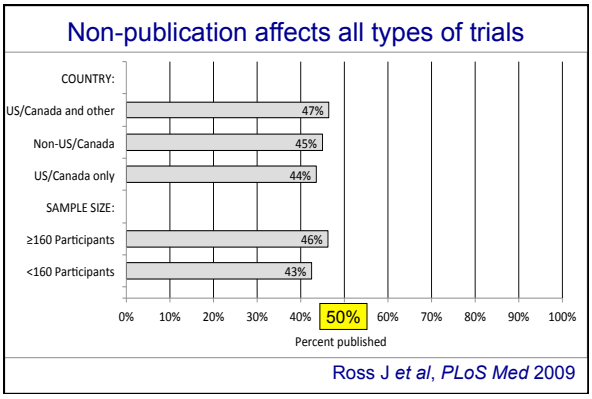
- >1000 trials completed per month
- >30,000 patients per month
  - Median published sample size = 52

"When I had to decide whether to have a 2nd bone marrow transplant, I found there were four trials that might have answered my questions, but I was forced to make my decision without knowing the results because, although the trials had been completed some time before, they had not been properly published! I believe that research results must be seen as a public good that belongs to the community – especially patients."

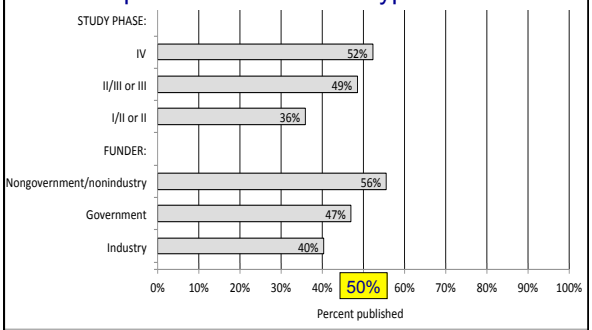
Alessandro Liberati, 2010


Protocol
Data forms
Raw dataset
Clean dataset
All results
Full study report
Published report
Registry
Abstract
100s-1000s of pages
<10 pages


Half of health research is unpublished
100%
80%
60%
40%
20%
0%
1980 - 1996
1997 - 2005
USA
UK
Australia
France
Denmark
Canada
Australia
Spain
UK
USA
Switzerl.
Germany
Spain
Netherl.
Song F et al, HTA 2010

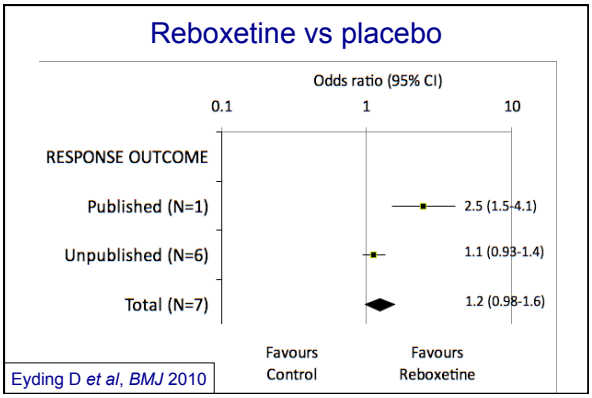

Non-publication affects all types of trials
COUNTRY:
US/Canada and other
47%
Non-US/Canada
45%
US/Canada only
44%
SAMPLE SIZE:
≥160 Participants
46%
<160 Participants
43%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Percent published
Ross J et al, PLoS Med 2009

Non-publication affects all types of trials



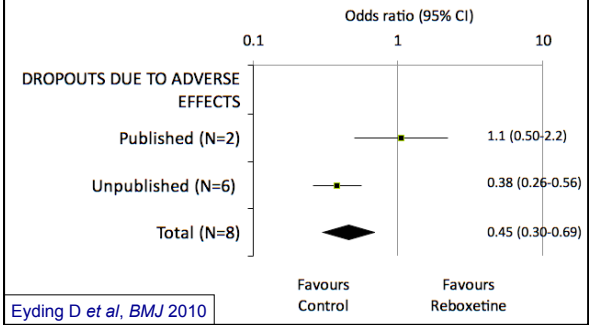
Ross J *et al*, *PLoS Med* 2009

Reboxetine vs placebo



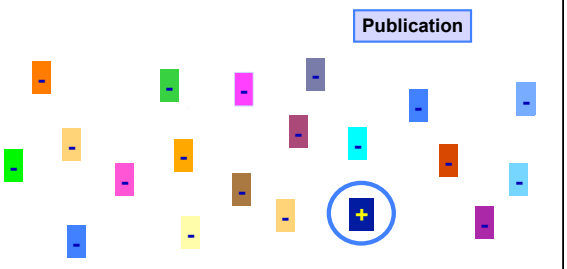
Eyding D *et al*, *BMJ* 2010

Reboxetine vs placebo



Eyding D *et al*, *BMJ* 2010

50% of trials change primary outcomes in retrospect



Dwan K, *PLoS One* 2013; Chan AW, *JAMA* 2004

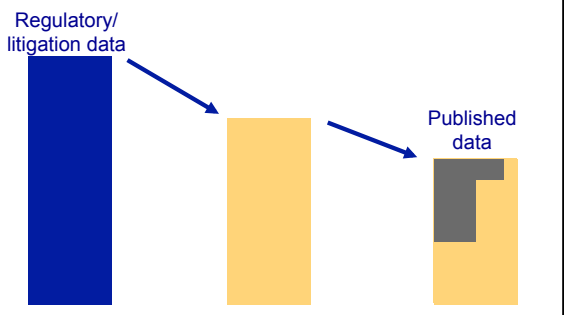
50% of trials change primary outcomes

Neurology trial
Surgical intervention

Protocol	Publication
Primary outcome: % with Score<3 at 1 year	Primary outcome: % dead/dependent at 1 year
P≥0.05	P<0.05

Chan AW *et al*, *JAMA* 2004 & *CMAJ* 2005; Redmond et al, *JCE* 2013

Evidence from regulators & litigation



Vedula S, *NEJM* 2009; Rising K, *PLoS Med* 2008; Turner EH, *NEJM* 2008

Patient morbidity and deaths

Rofecoxib	100,000 heart attacks in 1999-2004 (US)
Lorcainide	50,000 deaths per year in 1980s (US)

$$$ Billions wasted

- EU-funded health research from 1998-2006
  - 6 billion Euros ⟶ 50% unpublished

Galsworthy MJ *et al, Lancet* 2012

- Gabapentin
  - $2 billion in 2002 in US ⟶ 94% for off-label uses

Vedula S *et al, NEJM* 2009; *Trials* 2012

World Health Organization — INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM SEARCH PORTAL

http://www.who.int/trialsearch

ANZCTR Australian New Zealand Clinical Trials Registry

ClinicalTrials.gov A service of the U.S. National Institutes of Health

ISRCTN REGISTER

CLINICAL TRIALS REGISTRY-INDIA
NATIONAL INSTITUTE OF MEDICAL STATISTICS,(ICMR)

NEDERLANDS TRIAL REGISTER

ChiCTR 中国临床试验注册中心 Chinese Clinical Trial Register

Deutsches Register Klinischer Studien
German Clinical Trials Register

Value of trial registries

- Informed enrolment
- Track existing trials
- Transparency

Value of trial registries

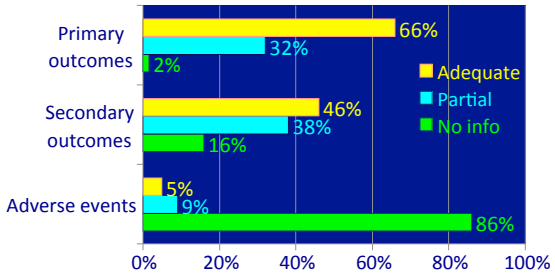
- Medical & surgical trials published in top journals (2007-2012)
- Comparison of trial registries versus journal articles
- 31-49% had discrepant primary outcomes

Hannink G *et al, Ann Surg* 2013;
Rosenthal R & Dwan K, *Ann Surg* 2013;
Mathieu S *et al, JAMA* 2009

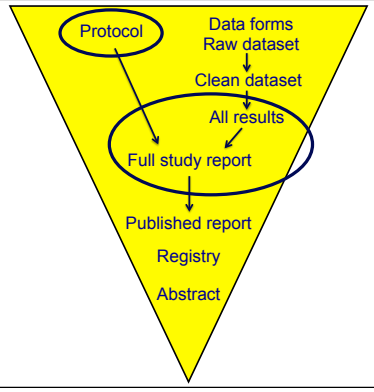
Limitations of trial registration

- Limited methodologic information
- No universal adherence mechanism
- Variable quality of registered information

Registration of outcomes (N = 265 & 237 trials)



Bourgeois FT *et al*, *Ann Intern Med* 2010;
Reveiz L *et al, PLoS One* 2010



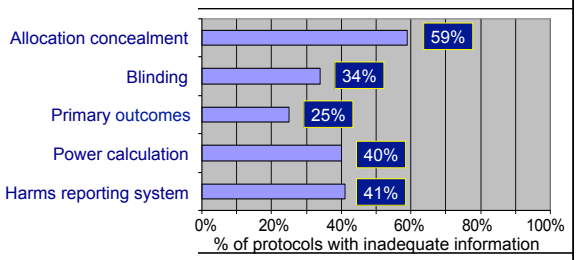
Access to protocols & full study reports

- Appraisal of study methods
- Identification of selective reporting
- Inform clinical care and future research

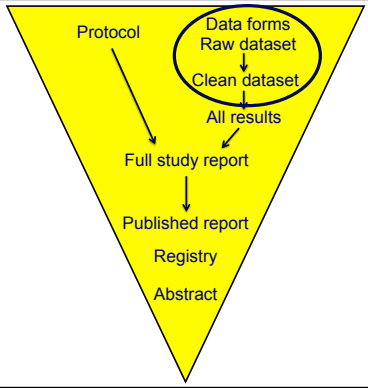
Current landscape

- Protocols and full study reports
  - Not publicly available
  - Variable quality
  - Variable standards

Protocols lack important information

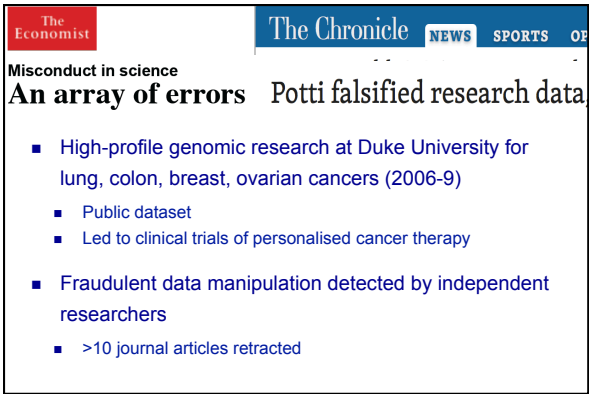


Hróbjartsson A *et al, J Clin Epid* 2009; Chan AW *et al*, *BMJ* 2008, *JAMA* 2004; Scharf O, *J Clin Oncol* 2006; Pildal J *et al*, *BMJ* 2005; Soares HP *et al*, *BMJ* 2004.



Benefits of sharing participant-level data

- Independent re-analysis
- Testing of secondary hypotheses
- Increased power of meta-analysis



- High-profile genomic research at Duke University for lung, colon, breast, ovarian cancers (2006-9)
  - Public dataset
  - Led to clinical trials of personalised cancer therapy
- Fraudulent data manipulation detected by independent researchers
  - >10 journal articles retracted

Current landscape

- Data sharing remains rare
  - Even when well-accepted (genomics) or mandated
- Multiple barriers
  - Time and effort to prepare annotated data sets
  - Lack of standard guidance for best practices

Recommendation 1 – Incentives

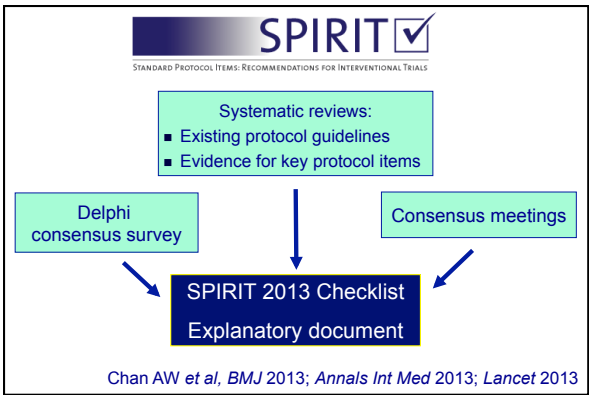
Adopt performance metrics recognising full dissemination

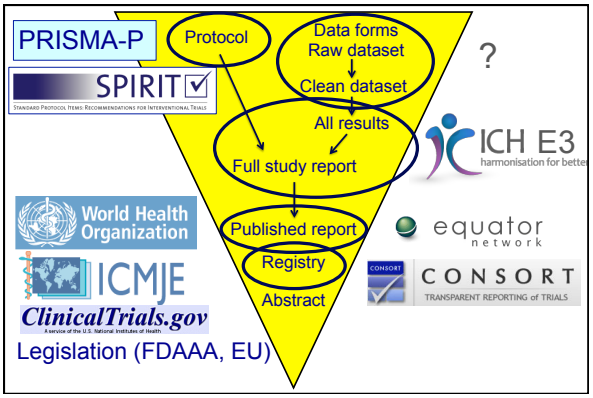
- % of funded/approved studies that are published
- % of protocols, full study reports, and datasets that are made available
- Dataset re-use by external researchers

Recommendation 2 – Best practices

Develop & adopt standards for protocols, full study reports, & data sharing

- Systematic development
- Adoption by investigators, funders, sponsors, regulators, research ethics committees, journals





Recommendation 3 – Adherence mechanisms

Enforce study registration, access to protocols & full study reports, and data sharing for all health research

- Endorsement and enforcement by funders, sponsors, regulators, research ethics committees, journals, legislators

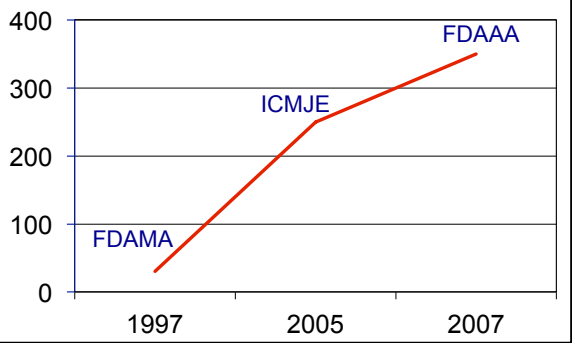
NHS Health Research Authority

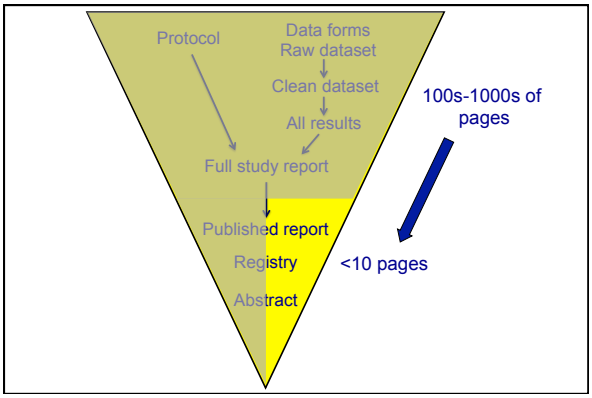
- Requires registration of all UK clinical trials as condition of ethics approval

NIHR Health Technology Assessment programme

- Publishes own journal
- Withholds 10% of funds
- 98% publication rate for completed studies

New registrations per week on CT.gov





Conclusions

- Majority of information on health research is inaccessible
- Impact on science, policy, patient care
- Action needed from key stakeholders
  - Incentives
  - Standards
  - Adherence mechanisms

What can patients do?

- Become informed
- Support transparency initiatives & legislation
- Insist on trial registration and dissemination before joining a trial