Transparency and access to clinical trial data

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Index

- Why trial transparency is necessary
- How to achieve it
- Obstacles

Why trial transparency is necessary

- Because I need to be able to trust what I read.
- This will dictate (in part) my subsequent actions as a physician

Cochrane reviews

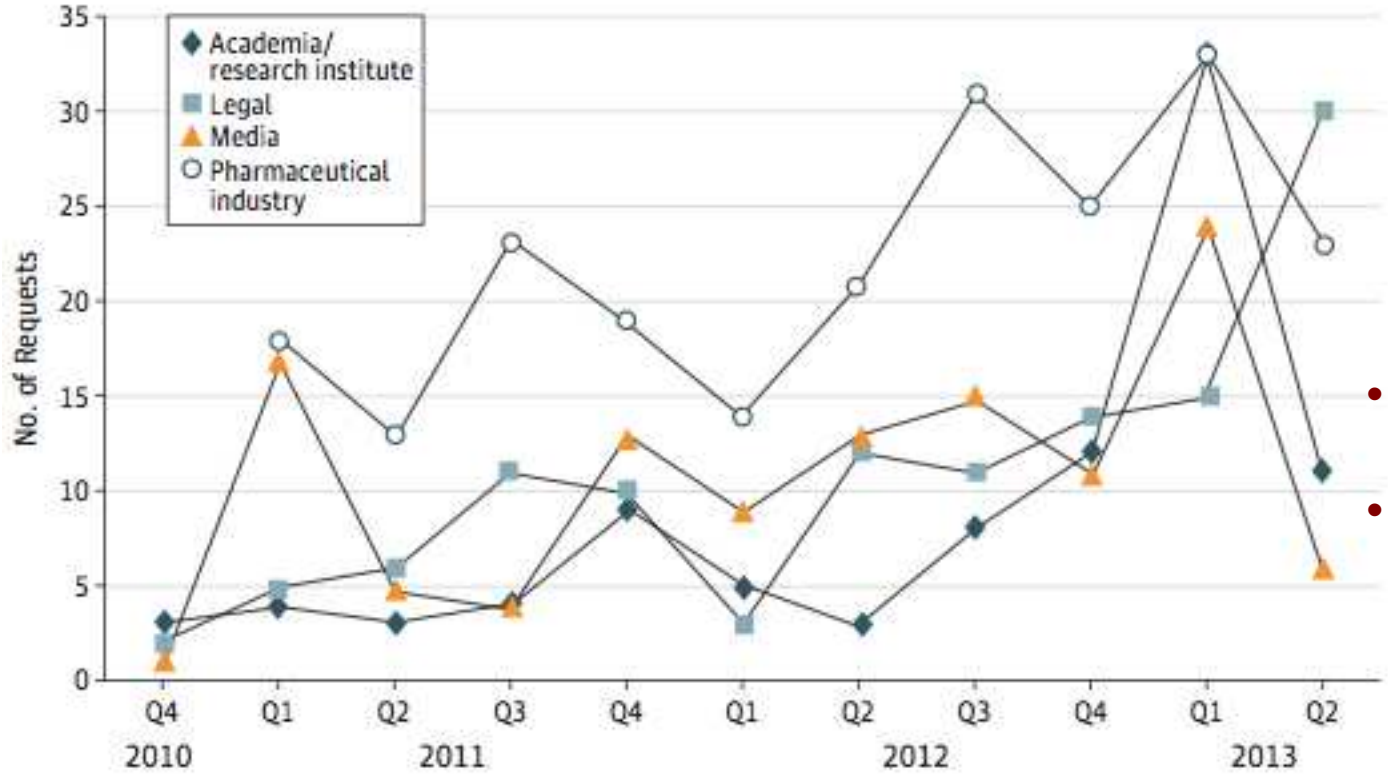
- Goal: to provide trusted evidence for informed decisions

- Major threats to systematic reviews
  - Unpublished trials
  - Misreporting of published trials
    - Misleading description of the study design, conduct and results of trials

Evidence of discrepancies

- At present there are 16 systematic reviews comparing regulatory information with register data and publication of the same trials across a wide range of interventions.
- All show major discrepancies, with CSRs seeming the most reliable and detailed

EMA retroactive release policy (0043)



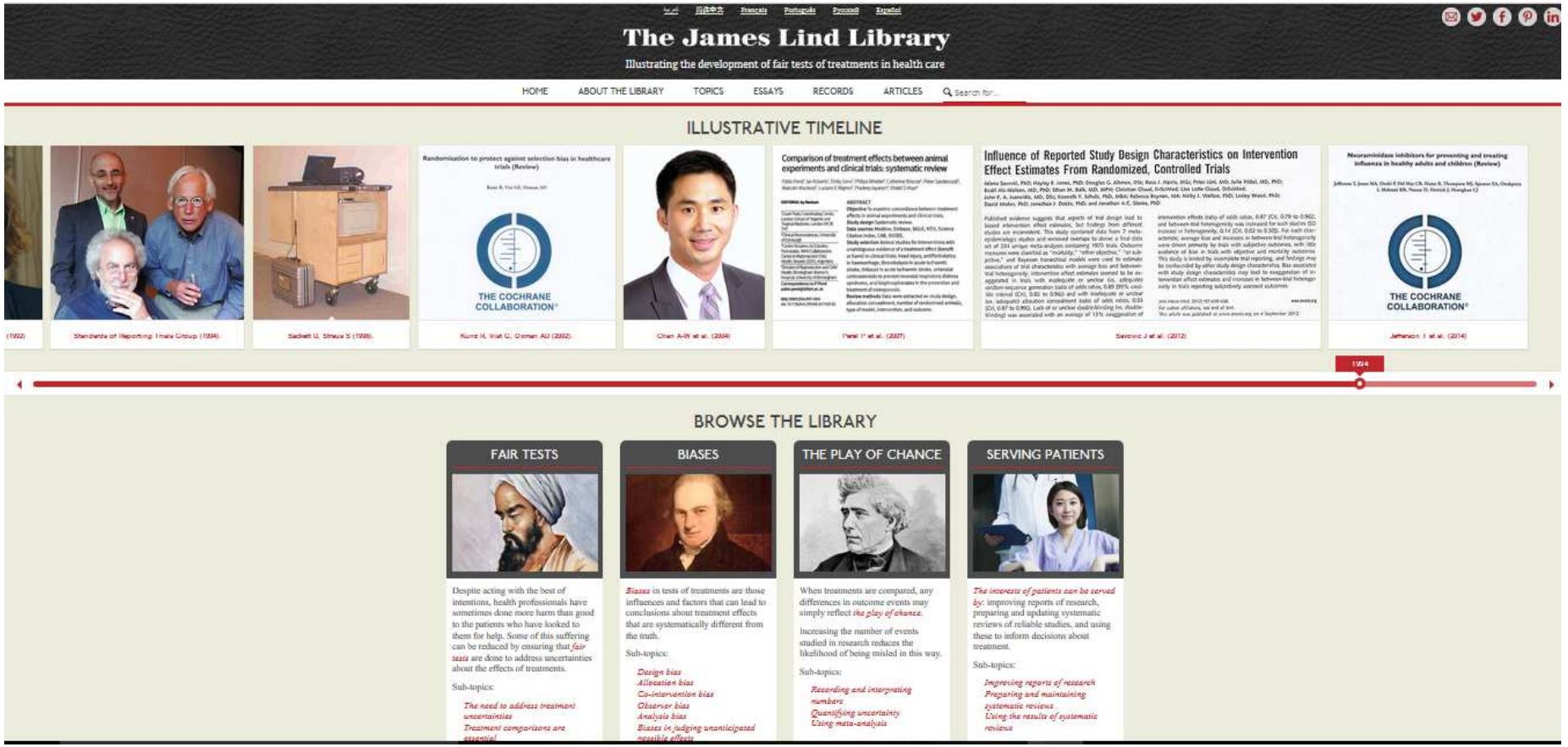
- Industry consistent top requestor of data
- Data also requested by regulators outside EU (Courtesy of Peter Doshi)

Figure. Requests for Documents Handled Under the European Medicines Agency's Policy Between November 30, 2010, and June 4, 2013

Types of regulatory documents

Item (RCT rel)	Acr	Length (pages)	Content	Source
Clinical Study Reports (Y)	CSR	1000s	IMRAD, protocol, amendments, SAP, listings	EMA*
Integrated Summary of Effectiveness or Safety (Y)	ISE ISS	100s?	Pooled or m-a summaries of data	EMA* (FDA)
Periodic Safety Update Reports /MedWatch (N)	PSUR	1000s/ database	Ph vigilance	EMA/ FDA
Drug Approval Packages (Y)	DAP	100s	Reviewers' reports + correspondence	FDA
Eur Public Assessm Reports (Y)	EPAR	10s	Summary of Cttee for Med Products for Human Use	EMA
Common Technical Document (Y)	CTD	100s	Overviews (2.5 & 2.7)	EMA*

Progress and evolution



Obstacles

- Publication mind set
- Critical appraisal industry
- Concealed or unconscious conflicts
- Commercial in confidence
- «The data are ours»
- Too much bother
- We have always done it this way
- Sheer ignorance of the problem
- Trust me, I am doctor

Redactions - a real threat

Case number°	Subject number	Treatment group	Date of Vacc 1	Sero status at M0	Cytology and PCR results at M0	Date of M6 visit	Cytology and PCR results at M6	Other cytology and PCR results from M12 onwards	Visit leading to biopsy	Clinical diagnosis and biopsy PCR results	Protocol defined case	HPV TAA case
[redacted]		HAV	08JUN2004	N	NI: -	10DEC2004	NA: -	M12 (21JUN2005): NI: HPV-51/53 M18 (01DEC2005): NA: HPV-16/53/74 M24 (08JUN2006): NI: HPV-16/51 M30 (07DEC2006): NA: HPV-16/51/74 M36 (28MAY2007): ASC-H: HPV-16/51/74 M42 (08JAN2008): NI: HPV-16 M48 (06JUN2008): NI: -	M42	08JAN2008: PUNCH 1A CIN2 HPV-16; 17MAR2008: LEEP 1B CIN2 HPV-16; 17MAR2008: LEEP 3A CIN2 HPV-16; 17MAR2008: LEEP 3B CIN2 HPV-16/51; 17MAR2008: LEEP 3C CIN2 HPV-16	HPV-16	HPV-16
		HAV	18AUG2004	N	NI: -	16FEB2005	NA: -	M12 (17AUG2005): NI: -	M42	11MAR2008:	HPV-16	HPV-16

Cervarix Trial HPV-008 – CSR main body pdf page 269/641

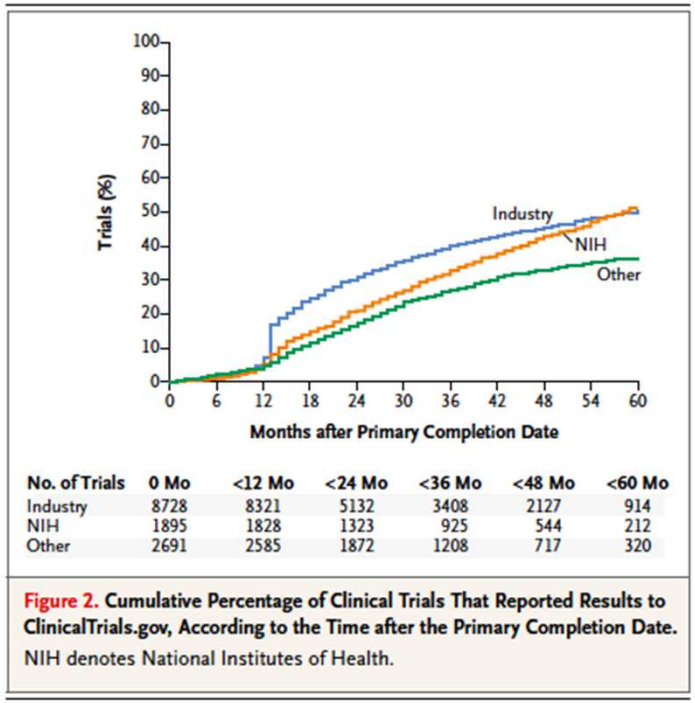
Conclusions

- Unpublished trials and misreporting of published trials are major threats to the validity of Cochrane Systematic Reviews.

- Access to regulatory documents such as Clinical Study Reports could be an important opportunity to overcome these issues

Unpublished trials

- 50% of completed clinical trials are published[1]
- Same proportion for 30 years
- Trials registration and legal requirements insufficient[2]
  - 13,327 completed trials subject to FDA Amendment Act provisions from 2008-2012
  - 13% posted results within 12 months after trial completion



No. of Trials	0 Mo	<12 Mo	<24 Mo	<36 Mo	<48 Mo	<60 Mo
Industry	8728	8321	5132	3408	2127	914
NIH	1895	1828	1323	925	544	212
Other	2691	2585	1872	1208	717	320

Figure 2. Cumulative Percentage of Clinical Trials That Reported Results to ClinicalTrials.gov, According to the Time after the Primary Completion Date.
NIH denotes National Institutes of Health.

[1] Chan AW, Lancet 2014
[2] Anderson NEJM 2015

Misreporting
Selective reporting of outcomes

- Comparison of outcomes reported in protocols and publications[1]
  - 50% of efficacy and 65% of harm outcomes per trial were incompletely reported with statistically significant outcomes having a higher odds of being fully reported.[2]
- A comparison of the primary outcomes registered and published[2]
  - discrepancies in 31% of RCTs.
- 50% of Cochrane reviews highly suspect of selective reporting of efficacy outcomes[3] and 63% of safety outcomes[4]
- A comparison of publication and registered
  - Serious adverse events completely reported in CT.gov 99% vs 63% in publication

[1] Chan AW. JAMA. 2004
[2] Mathieu S,. JAMA. 2009
[3] Kirkham, BMJ 2010
[4] Saini, BMJ, 2014
[3]Riveros Plos Med 2013