

# Transparency and access to clinical trial data

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# 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  - Unpublished trials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)

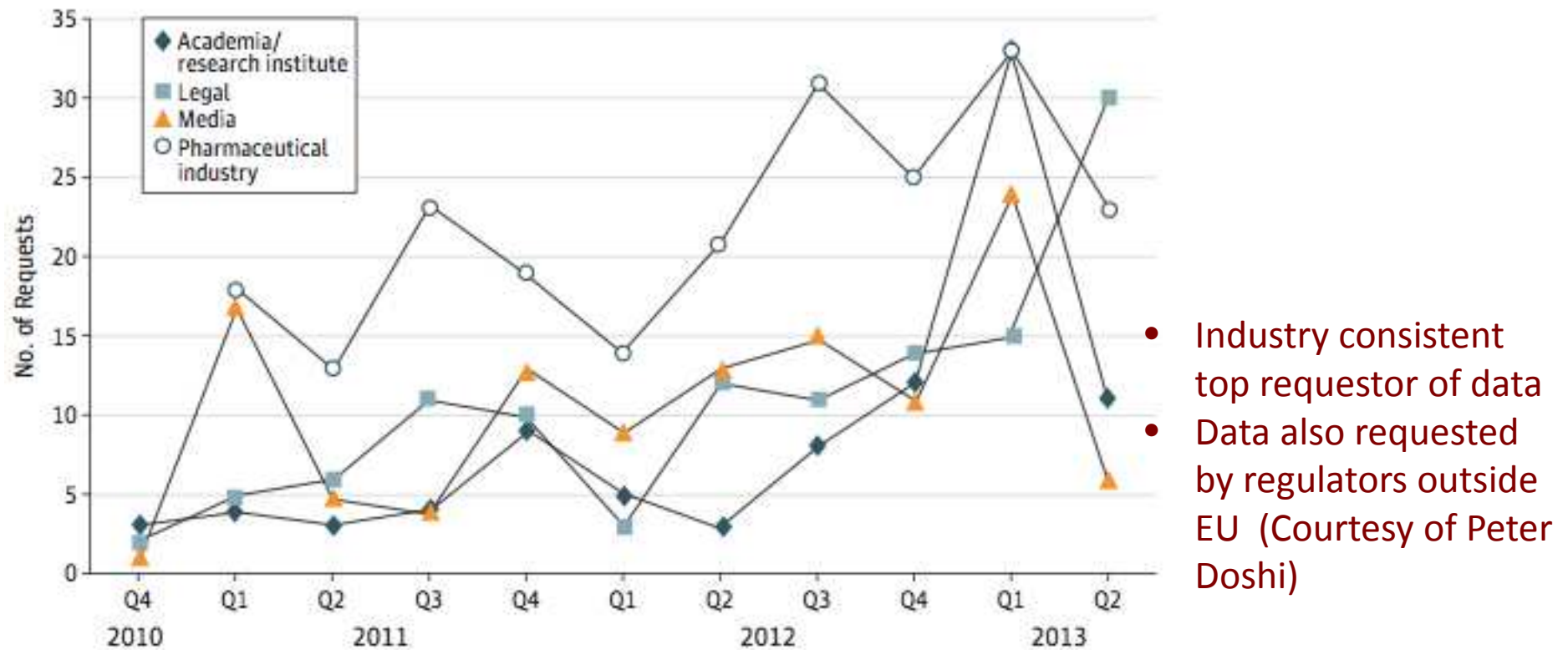


Figure. Requests for Documents Handled Under the European Medicines Agency's Policy

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

**The James Lind Library**  
Illustrating the development of fair tests of treatments in health care

HOME ABOUT THE LIBRARY TOPICS ESSAYS RECORDS ARTICLES

## ILLUSTRATIVE TIMELINE

Standards of Reporting Trial Group (1995)

Sackett U, Straus D (1998)

Kunz R, Vist G, Ozman AG (2002)

Chan A-W et al. (2004)

Farr P et al. (2017)

Sirovica J et al. (2012)

Jamaison J et al. (2014)

## BROWSE THE LIBRARY

### FAIR TESTS

Despite acting with the best of intentions, health professionals have sometimes done more harm than good in the patients who have looked to them for help. Some of this suffering can be reduced by ensuring that **fair tests** are done to address uncertainties about the effects of treatments.

Sub-topics:

- The need to address treatment uncertainties
- Treatment comparisons are essential

### BIASES

**Biases** in tests of treatments are those influences and factors that can lead to conclusions about treatment effects that are systematically different from the truth.

Sub-topics:

- Design bias
- Allocation bias
- Co-intervention bias
- Observer bias
- Analysis bias
- Biases in judging unanticipated possible effects

### THE PLAY OF CHANCE

When treatments are compared, any differences in outcome events may simply reflect **the play of chance**.

Increasing the number of events studied in research reduces the likelihood of being misled in this way.

Sub-topics:

- Recording and interpreting numbers
- Quantifying uncertainty
- Using meta-analysis

### SERVING PATIENTS

**The interests of patients can be served** by: improving reports of research, preparing and updating systematic reviews of reliable studies, and using these to inform decisions about treatment.

Sub-topics:

- Improving reports of research
- Preparing and maintaining systematic reviews
- Using the results of systematic reviews



# 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

580299/008 (HPV-008)

Report (M48)

Case number <sup>o</sup>	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
		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: - M18 (11 JAN 2006): NI: HPV-51	M42	11MAR2008: LEEP 3A CIN2	HPV-16	HPV-16

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

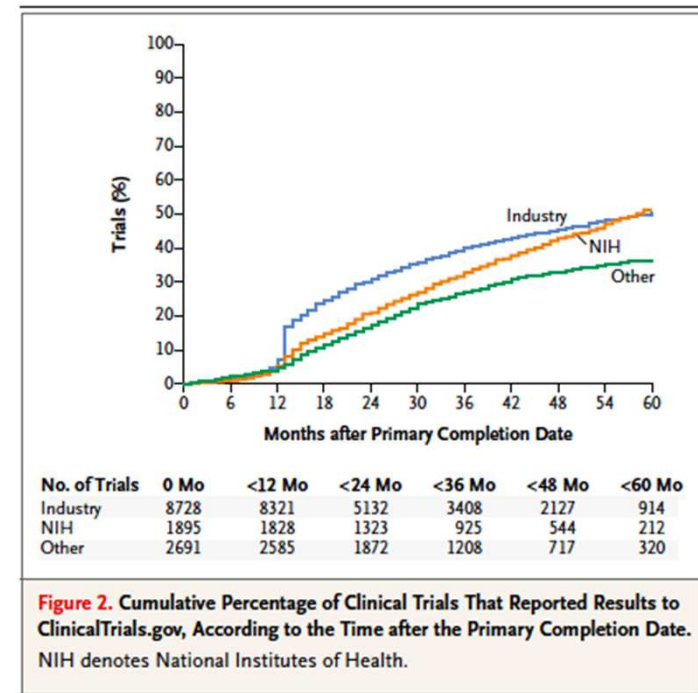
# Conclusions

- 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<sup>1</sup>
- Same proportion for 30 years
- Trials registration and legal requirements insufficient<sup>2</sup>
  - 13,327 completed trials subject to FDA Amendment Act provisions from 2008-2012
  - 13% posted results within 12 months after trial completion



<sup>1</sup> Chan AW, Lancet 2014

<sup>2</sup> Anderson NEJM 2015

# Misreporting

## Selective reporting of outcomes

- Comparison of outcomes reported in protocols and publications<sup>1</sup>
  - 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.<sup>2</sup>
- A comparison of the primary outcomes registered and published<sup>2</sup>
  - discrepancies in 31% of RCTs.
- 50% of Cochrane reviews highly suspect of selective reporting of efficacy outcomes<sup>3</sup> and 63% of safety outcomes<sup>4</sup>
- A comparison of publication and registered
  - Serious adverse events completely reported in CT.gov 99% vs 63% in publication

<sup>1</sup> Chan AW. JAMA. 2004

<sup>2</sup> Mathieu S,. JAMA. 2009

<sup>3</sup> Kirkham, BMJ 2010

<sup>4</sup> Saini, BMJ, 2014

<sup>3</sup>Riveros Plos Med 2013