# WE HAVE COME A LONG WAY

## DATA TRANSPARENCY AND PHARMACEUTICAL REGULATION IN EUROPE

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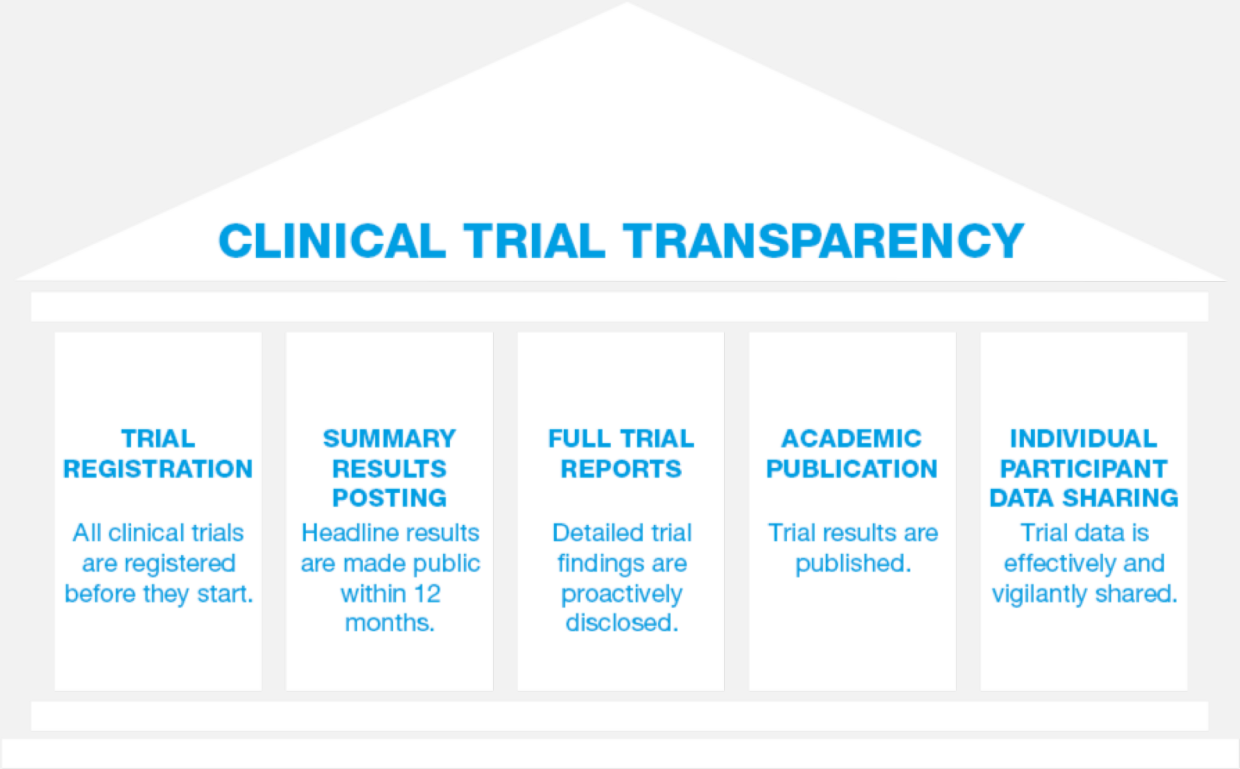
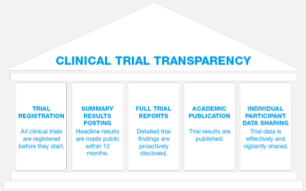
LUND UNIVERSITY

# TRANSPARENCY: SPONSORS & INVESTIGATORS




Source: Transparency International, Cochrane, CRIT and TranspariMED (2017)
Clinical Trial Transparency: A guide for policy makers




James Lind Alliance
Priority Setting Partnerships

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

BEUC
The European Consumer Organisation (BEUC)

TranspariMED
Working to end evidence distortion in medicine

+AllTrials

Medicines in Europe Forum

# WE HAVE COME A LONG WAY

- Policy initiatives have emerged over the course of the last 10 yrs. thanks to **concerted effort** on the part of civil society groups, professional organizations, academic journals, regulators, lawmakers, and individuals.

- The political significance of this development should not be underestimated since it shows that – with enormous determination, persistence, and vigilance – **a loose coalition of actors can achieve major policy gains.**

Cochrane

Cochrane Nordic

European Parliament

HAI HEALTH ACTION INTERNATIONAL

EUROPEAN MEDICINES AGENCY
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Prescrire

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*Joint Letter by the European Commission, EMA and HMA*

June 2019

**LETTER TO STAKEHOLDERS REGARDING THE REQUIREMENTS TO PROVIDE RESULTS FOR AUTHORISED CLINICAL TRIALS IN EUDRACT**

"Underreporting in general and selective reporting of trials with positive outcome...**compromise the economic and scientific efficiency of clinical research**. In addition, unreported clinical trials with unfavourable outcome can have **negative public health implications**."

# PUBLICATION BIAS IN 60'S AND 70'S

TABLE III—*Publishing status of controlled trials included in applications to licensing authorities. (Figures are numbers (%) of trials)*

| | Psychotropic drugs | | | |
|---|---|---|---|---|
| | 1974 and 1975 | | All years* | |
| | Finland | Sweden | Finland | Sweden |
| No of trials | 234 | 108 | 341 | 225 |
| Published in journal | 115 (49) | 59 (55) | 177 (52) | 88 (39) |
| Published elsewhere | 9 (4) | 2 (2) | 24 (7) | 16 (7) |
| Not published | 96 (41) | 42 (39) | 116 (34) | 99 (44) |
| Only summary available | 14 (6) | 4 (4) | 24 (7) | 23 (10) |

*Years studied were 1965, 1970, 1974, and 1975.

Hemminki. E (1980) *British Medical Journal*

**Approx. 40% of trials submitted to regulators went completely unpublished**

# TRIALS REGISTRY: PROPOSAL IN **1986**

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

## Publication Bias: The Case for an International Registry of Clinical Trials

By Robert John Simes

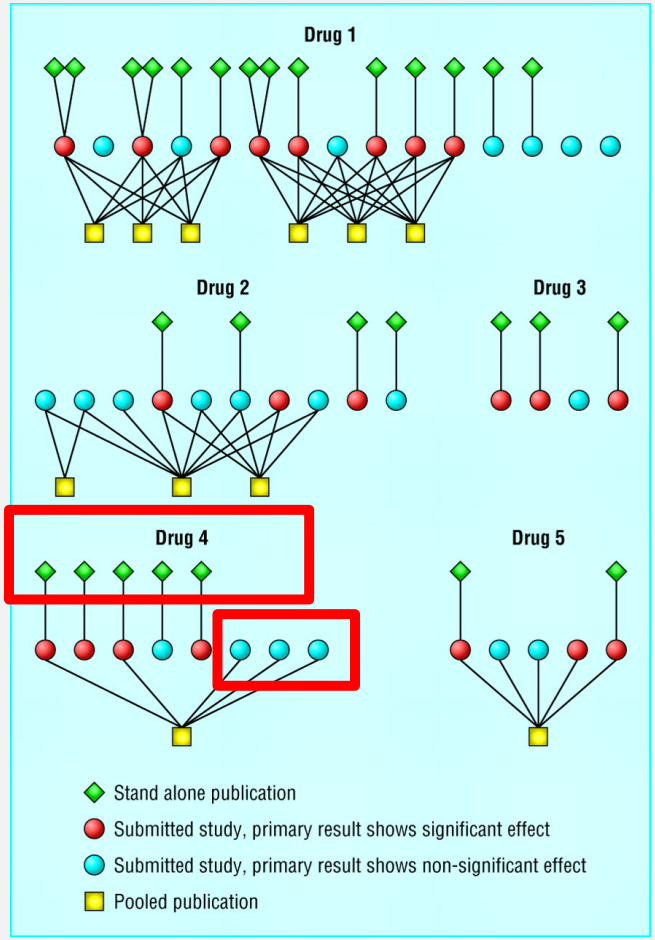
A problem in evaluating different therapies from a review of clinical trials is that the published clinical trial literature may be biased in favor of positive or promising results. In this report, a model is proposed for reviewing clinical trial results which is free from publication bias based on the selection of trials registered in advance in a registry. The value of a registry is illustrated by comparing a review of *published* clinical trials located by a literature search with a review of *registered* trials contained in a cancer trials registry. Two therapeutic questions are examined: (1) the survival impact of initial alkylating agent (AA) *v* combination chemotherapy (CC) in advanced ovarian cancer, and (2) the survival impact of AA/prednisone *v* CC in multiple myeloma. In advanced ovarian cancer, a pooled analysis of published clinical trials demonstrates a significant survival advantage for combination chemotherapy (median survival ratio of CC to AA, 1.16; $P = .02$). However, no significant difference in survival is demonstrated based on a pooled analysis of registered trials (median survival ratio, 1.05; $P = .25$). For multiple myeloma, a pooled analysis of published trials also demonstrates a significant survival advantage for CC (median survival ratio, 1.26; $P = .04$), especially for poor risk patients (ratio, 1.66; $P = .002$). A pooled analysis of registered trials also shows a survival benefit for patients receiving combination chemotherapy (all patients, $P = .06$; poor risk, $P = .03$), but the estimated magnitude of the benefit is reduced (all patients: ratio, 1.11; poor risk: ratio, 1.22). These examples illustrate an approach to reviewing the clinical trial literature, which is free from publication bias, and demonstrate the value and importance of an international registry of all clinical trials.

*J Clin Oncol 4:1529–1541.* 

Proposed **international registration of all clinical trials** after he showed that **conclusions about treatments for ovarian cancer and multiple myeloma differed depending on whether the results of unpublished trials had been taken into account.**

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# PUBLICATION AND REPORTING BIAS IN THE 90'S




"Without **access to all studies** (positive as well as negative, published as well as unpublished) and without **access to alternative analyses** (intention to treat as well as per protocol), any attempt to recommend a specific drug is likely to be based on **biased evidence**."

**Evidence b(i)ased medicine**

Melander. H, et al. (2003) *British Medical Journal*

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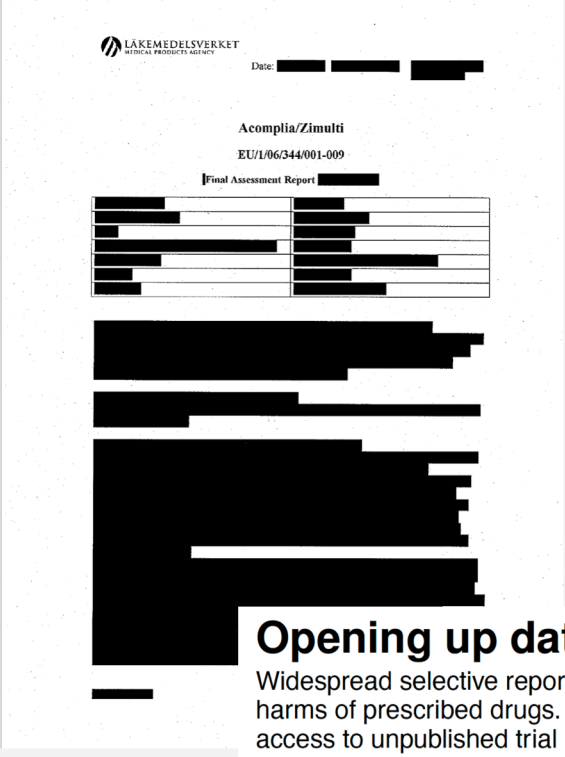
# CHALLANGING REGULATORY SECRECY IN THE EU (2007-2010)

Prescrire

Cochrane Nordic


LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Date: [redacted]

Acomplia/Zimulti

EU/1/06/344/001-009

Final Assessment Report [redacted]

[redacted]


[redacted]

BMJ

*BMJ* 2011;342:d2686 doi: 10.1136/bmj.d2686

## Opening up data at the European Medicines Agency

Widespread selective reporting of research results means we don't know the true benefits and harms of prescribed drugs. **Peter Gøtzsche** and **Anders Jørgensen** describe their efforts to get access to unpublished trial reports from the European Medicines Agency

Peter C Gøtzsche *professor*, Anders W Jørgensen *PhD student*

Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Dept 3343, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

# TURNING POINT I

European Ombudsman

**Ombudsman: European Medicines Agency should disclose clinical reports on anti-obesity drugs**

Press release no. 13/2010 - 07/06/2010

"The Ombudsman therefore found that EMA's refusal to grant access to the requested documents constituted an **instance of maladministration**."

30 November 2010
EMA/718259/2010
Press Office

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

**Press release**

## European Medicines Agency widens public access to documents

Policy on access to documents also sets out new approach for proactive disclosure of documents

# TURNING POINT II



**The campaign:**

- Facilitated the first ever Cochrane review (2009-2014) based entirely on clinical study reports and regulatory data.
- Led to changes in transparency by pharmaceutical companies and triggered inquiries at the national and international level.
- Heightened awareness of the importance of independent access to underlying trial data.

# ALL TRIALS CAMPAIGN (SINCE 2013)

- All planned trials to be **registered**, with a summary of the trial protocol, before the first participant is recruited
- A **summary of results** to be made publicly available where the trial was registered, within 1 year of completion
- **Full reports** made publicly available by regulators and industry

**The AllTrials petition has been signed by 95439 people and 747 organisations**

European Parliament

# FINALLY: PUBLIC CLINICAL TRIALS REGISTRY (2014)

The year 2014 saw the adoption of a new EU Regulation that requires **clinical trials to be registered in a publicly accessible database before the trial starts and mandates publication of summary results within a year after completion**

# GOOD VS. POOR REPORTING IN EU

**Table 4** Sponsors with highest proportion of trials reported

| Sponsor | Total trials on EUCTR | Due trials | Due trials with results | % reported |
|---|---|---|---|---|
| Gilead Sciences | 213 | 31 | 31 | 100.0 |
| Chiesi Farmaceutici | 94 | 37 | 37 | 100.0 |
| CSL Behring | 72 | 25 | 25 | 100.0 |
| Alcon | 71 | 20 | 20 | 100.0 |
| Genentech | 63 | 18 | 18 | 100.0 |
| Vertex Pharmaceuticals | 62 | 19 | 19 | 100.0 |
| Daiichi Sankyo | 62 | 12 | 12 | 100.0 |
| Almirall | 53 | 37 | 37 | 100.0 |
| Ferring Pharmaceuticals | 53 | 19 | 19 | 100.0 |
| Sanofi | 573 | 111 | 110 | 99.1 |
| Bayer | 274 | 72 | 71 | 98.6 |
| Johnson and Johnson | 424 | 108 | 106 | 98.1 |
| Novo Nordisk | 202 | 52 | 51 | 98.1 |
| Servier Laboratories | 134 | 48 | 47 | 97.9 |
| Novartis Vaccines | 142 | 44 | 43 | 97.7 |
| Abbvie | 179 | 33 | 32 | 97.0 |
| H Lundbeck | 76 | 29 | 28 | 96.6 |
| Astrazeneca | 520 | 141 | 136 | 96.5 |
| Otsuka | 58 | 27 | 26 | 96.3 |
| Amgen | 244 | 51 | 49 | 96.1 |
| Pfizer | 744 | 168 | 161 | 95.8 |
| Takeda | 172 | 47 | 45 | 95.7 |
| Astellas | 137 | 23 | 22 | 95.7 |
| Bristol-Myers Squibb | 314 | 36 | 34 | 94.4 |
| Eisai | 113 | 13 | 12 | 92.3 |
| Boehringer Ingelheim | 340 | 90 | 83 | 92.2 |
| Biogen | 103 | 35 | 32 | 91.4 |
| Merck | 662 | 164 | 146 | 89.0 |
| GlaxoSmithKline | 1060 | 293 | 260 | 88.7 |

**Table 5** Sponsors with highest proportion of trials unreported

| Sponsor | Total trials on EUCTR | Due trials with results | Due trials | % reported |
|---|---|---|---|---|
| Hospitals of Paris | 194 | 0 | 7 | 0.0 |
| Karolinska Institutet | 189 | 0 | 21 | 0.0 |
| Radboud University | 178 | 0 | 3 | 0.0 |
| Charité-Universitätsmedizin Berlin | 177 | 0 | 63 | 0.0 |
| Erasmus University | 161 | 0 | 3 | 0.0 |
| University of Amsterdam | 153 | 0 | 4 | 0.0 |
| Agostino Gemelli University Polyclinic | 142 | 0 | 11 | 0.0 |
| Ghent University | 126 | 0 | 19 | 0.0 |
| VU University Medical Centre | 126 | 0 | 3 | 0.0 |
| Utrecht University | 122 | 0 | 6 | 0.0 |
| AOU di Bologna, Policlinico S.Orsola-Malpighi | 120 | 0 | 1 | 0.0 |
| Helsinki University | 101 | 0 | 12 | 0.0 |
| Université libre de Bruxelles | 85 | 0 | 3 | 0.0 |
| Vita-Salute San Raffaele University | 83 | 0 | 5 | 0.0 |
| Hospices Civils de Lyon | 81 | 0 | 3 | 0.0 |
| Heidelberg University | 75 | 0 | 17 | 0.0 |
| University of Oslo | 72 | 0 | 1 | 0.0 |
| University of Munich (Ludwig-Maximilians) | 71 | 0 | 26 | 0.0 |
| Maastricht University | 61 | 0 | 2 | 0.0 |
| Fundació Clínic per a la Recerca Biomèdica | 60 | 0 | 1 | 0.0 |
| University of Cologne | 57 | 0 | 18 | 0.0 |
| Gothenburg University | 56 | 0 | 6 | 0.0 |
| Uppsala University/Uppsala County Council | 55 | 0 | 6 | 0.0 |
| Manchester University NHS Foundation Trust | 54 | 0 | 13 | 0.0 |

Goldacre B, DeVito NJ, Heneghan C, et al. (2018) *British Medical Journal*

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*Joint Letter by the European Commission, EMA and HMA*

June 2019

**LETTER TO STAKEHOLDERS REGARDING THE REQUIREMENTS TO PROVIDE RESULTS FOR AUTHORISED CLINICAL TRIALS IN EUDRACT**

**1. Reporting is a legal obligation**

"As of July 2014, result-related information should be posted within one year (6 months for paediatric trials) after the end of a clinical trial. The submission of the results to EudraCT is the **direct responsibility of the sponsors**."

**2. Non-commercial sponsors lag behind**

"As of April 2019…**31.8%** (5,855) of the trials have **missing results**. This is an encouraging trend, though there is still significant progress to be made. In particular, the reporting compliance for non-commercial sponsors is much lower than for commercial sponsors (77.2% for commercial sponsors vs **23.6% for non-commercial sponsors**)."

# THANK YOU & ACKNOWLEDGMENTS

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- The Faculty of Medicine, Lund University
- Cochrane Sweden
- Courtney Davis,  Kings College London, UK
- Tom Jefferson, University of Oxford, UK; Nordic Cochrane Centre, Denmark


**New book edited by *Katherine Fierlbeck, Janice Graham, and Matthew Herder***

**Chapter on "Data Transparency and Pharmaceutical Regulation in Europe: Road to Damascus, or Room without a View?"**

***Courtney Davis, Shai Mulinari, and Tom Jefferson***