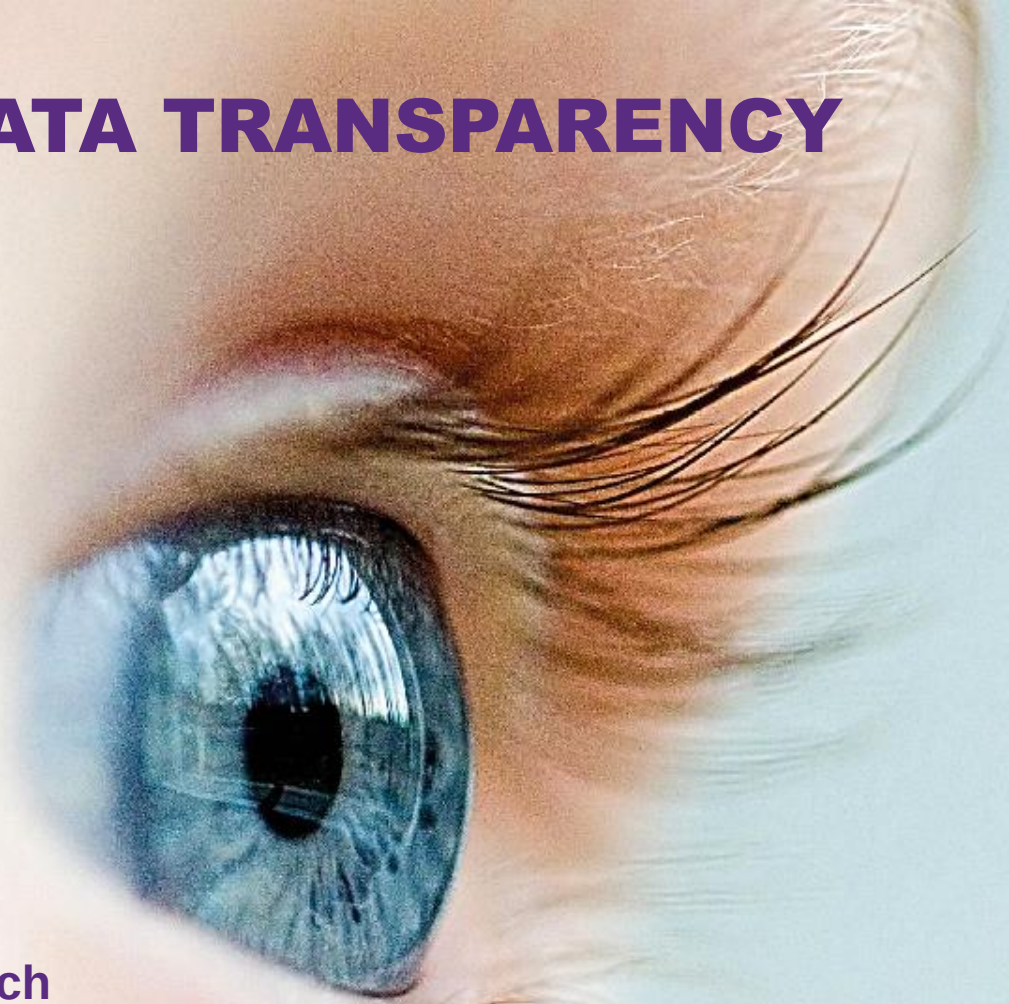
DATA SHARING & DATA TRANSPARENCY

An introduction



PSDM
Pharmaceutische Statistiek en Data Management

Egbert Biesheuvel, Nutricia Research

Stefan Driessen, Abbott Healthcare Products BV

1 December 2016

Abbott

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DISCLAIMER

The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the corresponding companies

CONTENTS – introduction

- **Early days of Transparency**
  - Registries
  - US Legislation
  - Industry Guidance
- **Recent days of Transparency**
  - EMA policy
  - PhRMA/EFPIA Principles
- **Today**

EARLY CALL FOR TRANSPARENCY – FDA 1997

Food and Drug Administration Modernization Act of 1997 (FDAMA)

Section 113 of FDAMA mandated the creation of a clinical trials database to register clinical trials of investigational drugs for "serious or life-threating diseases and conditions" (November 1997).

(3) The data bank shall include the following:

(A) A registry of clinical trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act, which provides a description of the purpose of each experimental drug, either with the consent of the protocol sponsor, or when a trial to test effectiveness begins. Information provided shall consist of eligibility criteria for participation in the clinical trials, a description of the location of trial sites, and a point of contact for those wanting to enroll in the trial, and shall be in a form that can be readily understood by members of the public. Such information shall be forwarded to the data bank by the sponsor of the trial not later than 21 days after the approval of the protocol.

EARLY CALL FOR TRANSPARENCY – 2004

- GlaxoSmithKline sued for concealing negative information about the antidepressant medication paroxetine
  - In **August 2004, GSK** agreed to post on its corporate Website a summary of clinical-study reports for every company-sponsored trial of its medications completed after December 27, 2000

- In **September 2004, Forest Laboratories**, which manufactures the anti-depressant medications citalopram and escitalopram, agreed to post on its corporate Website summaries of the results of clinical studies of marketed drugs completed after January 1, 2000

  This followed enquiries into the off-label use of anti-depressant drugs GlaxoSmithKline sued for concealing negative information about the antidepressant medication paroxetine

EARLY CALL FOR REGISTRATION – 2004

Clinical trial registration: a statement from the International Committee of Medical Journal Editors

Catherine De Angelis, Jeffrey M. Drazen, Frank A. Frizelle, Charlotte Haug, John Hoey, Richard Horton, Sheldon Kotzin, Christine Laine, Ana Marusic, A. John P.M. Overbeke, Torben V. Schroeder, Hal C. Sox, Martin B. Van Der Weyden

JAMC • 14 SEPT. 2004; 171 (6)

Registration is only part of the means to an end; that end is full transparency with respect to performance and reporting of clinical trials. Research sponsors may argue that public registration of clinical trials will result in unnecessary bureaucratic delays and destroy their competitive edge by allowing competitors full access to their research plans. We argue that enhanced public confidence in the research enterprise will compensate for the costs of full disclosure. Patients who volunteer to participate in clinical trials deserve to know that their contribution to improving human health will be available to inform health care decisions. The knowledge made possible by their collective altruism must be accessible to everyone. Required trial registration will advance this goal.

REGISTRATION of Protocols & Results - 2005

Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases[1]

Updated November 10, 2009

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

efpia European Federation of Pharmaceutical Industries and Associations

JPMA

PhRMA

Clinical Trial Register

All clinical trials[3] in patients conducted on a medicinal product at a minimum should be submitted for listing.

No later than 21 days after the initiation of patient enrollment, without prejudice to national legal requirements.

Clinical Trial Results

a. The results of all clinical trials[3] in patients at a minimum, conducted on a medicinal product that has been approved for marketing and is commercially available in at least one country should be publicly disclosed, regardless of outcome.

The results should be posted no later than one year after the medicinal product is first approved and commercially available in any country.

CLINICAL TRIAL REGISTRIES

REGISTER - Trial Initiation

Law

• FDAMA 113	1997
• State of Maine	2007
• FDAA Act of 2007	2007

Guidance

• WHO	2005
• EFPIA/PhRMA/JPMA	2005
• ICMJE	2005

Register Protocol Information
Publicly, e.g., ClinicalTrials.gov (Feb 2000)
Within 21 days of FPFV

RESULT DATABASE - Trial Completion

Law

• State of Maine	2007
• FDAA Act of 2007	2007

Guidance

• PhRMA	2002
• EFPIA/PhRMA/JPMA	2005
• ICMJE	2005

Post Trial Results marketed drugs
Sponsor website / ClinicalStudyResults.org
Within 1 year after LPLV

PROTOCOL REGISTRATION – WHAT TO POST
NEJM/WHO minimal data set (#20)

1. Unique trial number
2. Trial registration date
3. Secondary IDs
4. Funding source(s)
5. Primary sponsor
6. Secondary sponsor(s)
7. Responsible contact person
8. Research contact person
9. Title of the study
10. Official scientific title of study
11. Research ethics review
12. Condition
13. Intervention(s)
14. Key in- and exclusion criteria
15. Study type
16. Anticipated trial start date
17. Target sample size
18. Recruitment status
19. Primary outcome
20. Key secondary outcomes

RESULTS DATABASE – WHAT TO POST

What to post:

- Participant Flow
- Baseline Characteristics
- Outcome Measures and Statistical Analyses
- Adverse Events

How to post:

- Strict formats; review cycle; PRS system

LEGAL CALL FOR TRANSPARENCY – 2007

EU OMBUDSMAN

- In **2007**, **Danish researchers turned to EMA** and requested access to clinical study reports for two anti-obesity drugs
  - wanted to conduct an independent analysis, given that, in their view, biased reporting on drug trials was common
- EMA refused disclosure because it would undermine drug producers' commercial interests.
- EU Ombudsman called on EMA to disclose the documents or provide a convincing explanation as to why no access could be given.
- EMA decided to grant access to the documents requested
- EMA further committed itself to **reactive disclosure**

PARADIGM SHIFT - EMA INITIATIVE - April 2012

OPEN ACCESS Freely available online

PLoS MEDICINE

Perspective

Open Clinical Trial Data for All? A View from Regulators

Hans-Georg Eichler[1]*, Eric Abadie[1,2], Alasdair Breckenridge[3], Hubert Leufkens[1,4], Guido Rasi[1]

1 European Medicines Agency (EMA), London, United Kingdom, **2** Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) Saint-Denis, France, **3** Medicines and Healthcare products Regulatory Agency (MHRA), London, United Kingdom, **4** Medicines Evaluation Board (CBG-MEB), Den Haag, The Netherlands

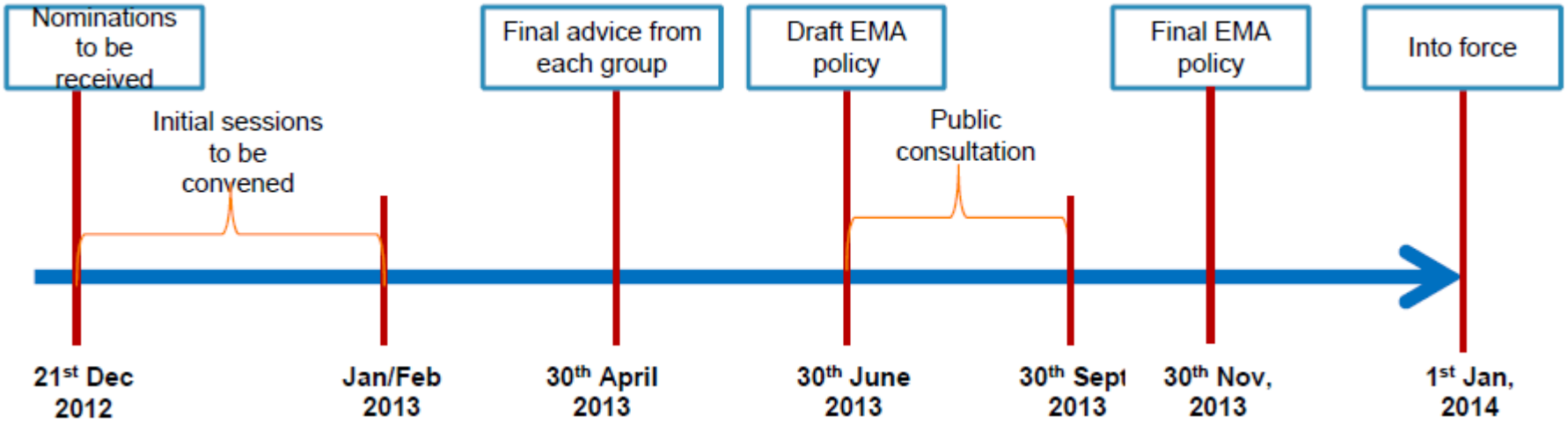
News

11/04/2012

European regulators propose way forward for publication of full clinical-trial data

A group of European regulators have set out a way forward for the publication of the results of clinical trials of authorised medicines. 'Open clinical trial data for all? A view from regulators', published yesterday in the journal *PLoS Medicine*, responds to an article in the same issue by Doshi and colleagues, which calls for open access to all clinical-trial data so that independent re-analysis of medicines' benefits and risks can be conducted.

EMA'S ROAD TO TRIAL DATA DISCLOSURE



- **Announcement** **April 2012**
- **Draft EMA policy** **June 24th 2013**
- **Consultation until** **September 30th 2013**

1,138 comments submitted by 169 entities

- **Final EMA policy** ~~**November 30th 2013**~~ **October 2nd 2014**

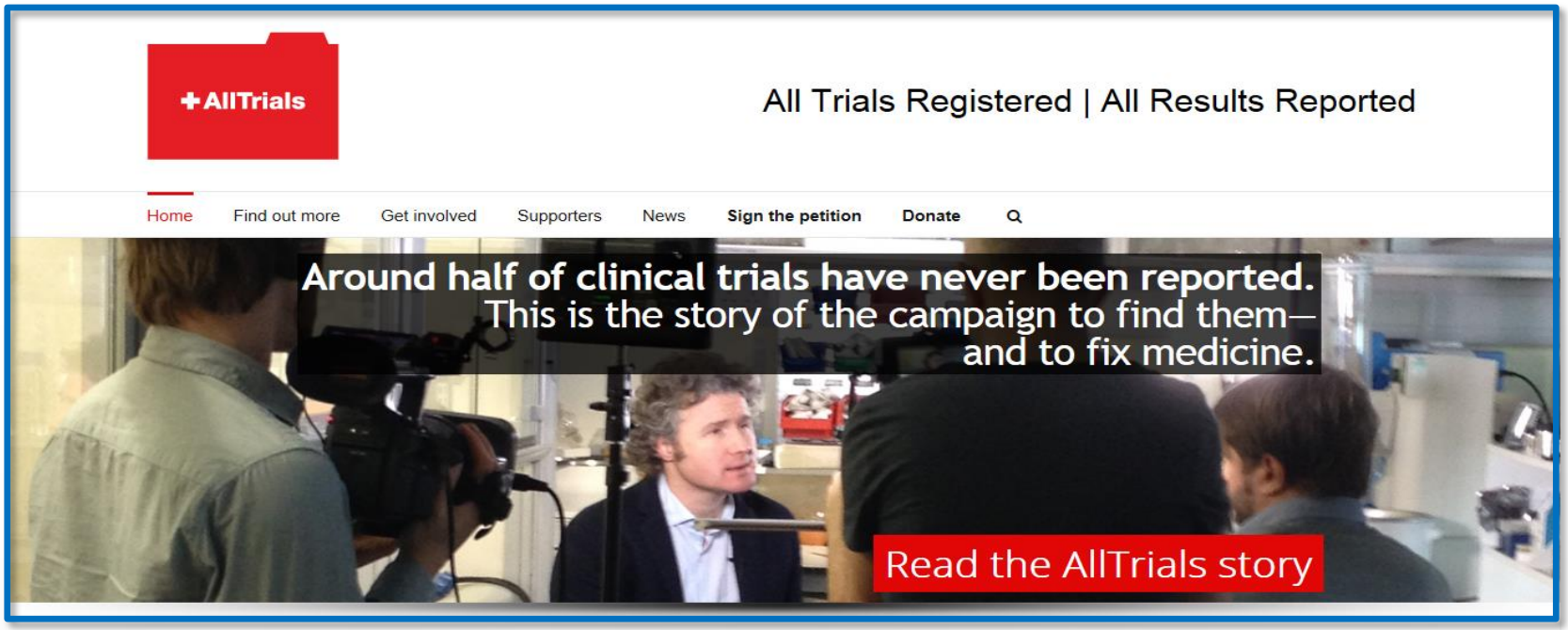
EMA FINAL POLICY – SUMMARY

- **Effective: submissions after Jan 1st 2015 (new products)**
  Jul 1st 2015 (line extensions)
- **Scope: centralized procedure only**
- **Publication of Clinical Reports (modules 2.5/ 2.7/ 5)**
  - Redacted for data protection & commercial confidential information
  - Redaction to be approved by EMA
  - Publication upon approval:

- **Release of patient level data postponed**
  - Stakeholder discussion planned, revision of policy thereafter

PUBLIC DEMAND FOR TRANSPARENCY

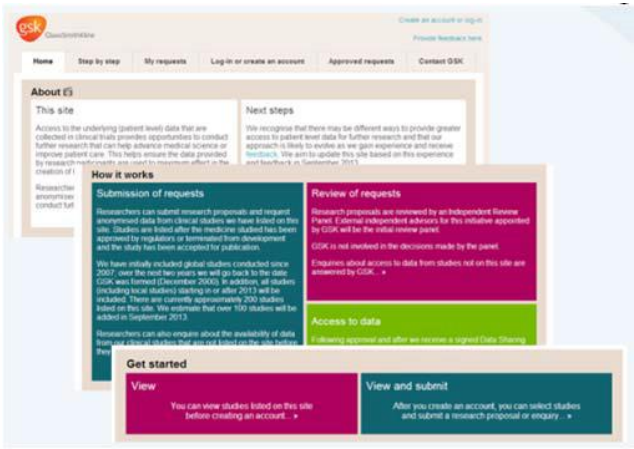
- **The ALLTRIALS Campaign, launched January 2013**



the AllTrials petition has been signed by 89507 people and 705 organisations

INDUSTRY'S REACTION - 2013

- **GSK: Clinical Study Requests website released: May 2013**
  (*https://clinicalstudydata.gsk.com/ sep2013)*



- Many others joined

- **Resulted in a joined website:**

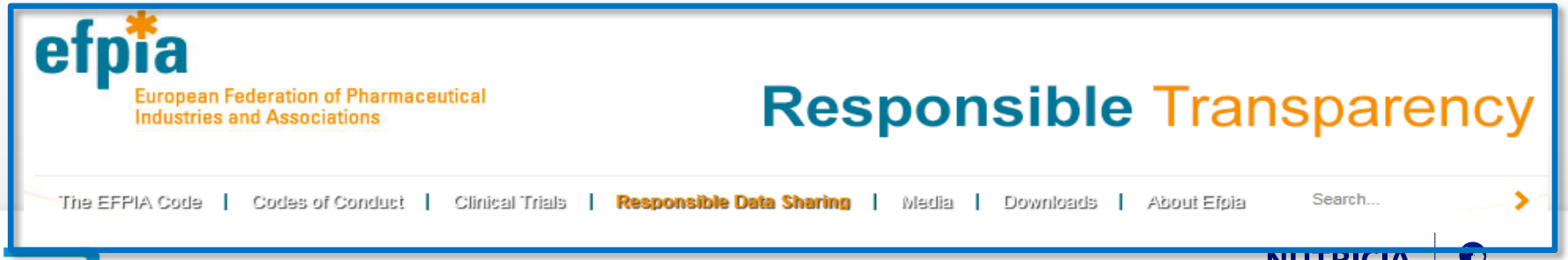
ClinicalStudy DataRequest.com

- **Two companies brought cases to Court**
  EMA has been ordered by the General Court of the European Union not to provide documents until a final ruling is given

INDUSTRY'S REACTION - 2013

- **PhRMA/EFPIA: "Principles for Responsible Clinical Trial Data Sharing"** (July 2013, effective 2014)
- Released 24 Jul 2013

- **May 2014: EFPIA launches clinical trial data portal gateway**
  - Provides links to policies of companies for Data Sharing
  - Companies have adopted different approaches to comply with the Principles

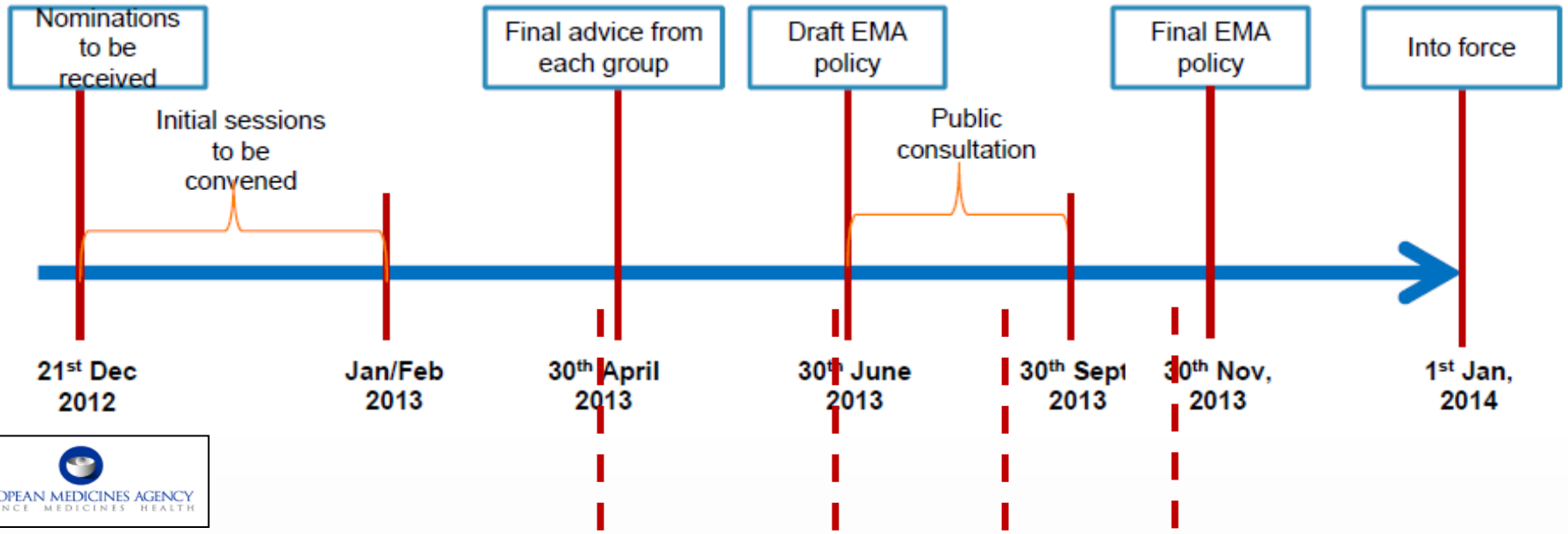


PhRMA/EFPIA PRINCIPLES – 5 Commitments

1. **Clinical Data Sharing**, Study Protocol and Study Report under **Controlled Access** governed by an Independent Board
2. Making available **publicly study synopses**
3. Making available to patients that participated in the trial a summary of the findings of that trial
4. Certification of the processes concerned and making that publicly available
5. Publication of results of phase 3 trial or other trial with medical important findings *(reiteration)*

- Applicable to all submissions to FDA, **EMA, or EU NC**
- As of **01 JAN 2014**, and within reasonable time after approval product and indication

EFSPI



EUROPEAN MEDICINES AGENCY
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EFSPI

2012-2013 — Participant contributions

April 2013 — Position Statement

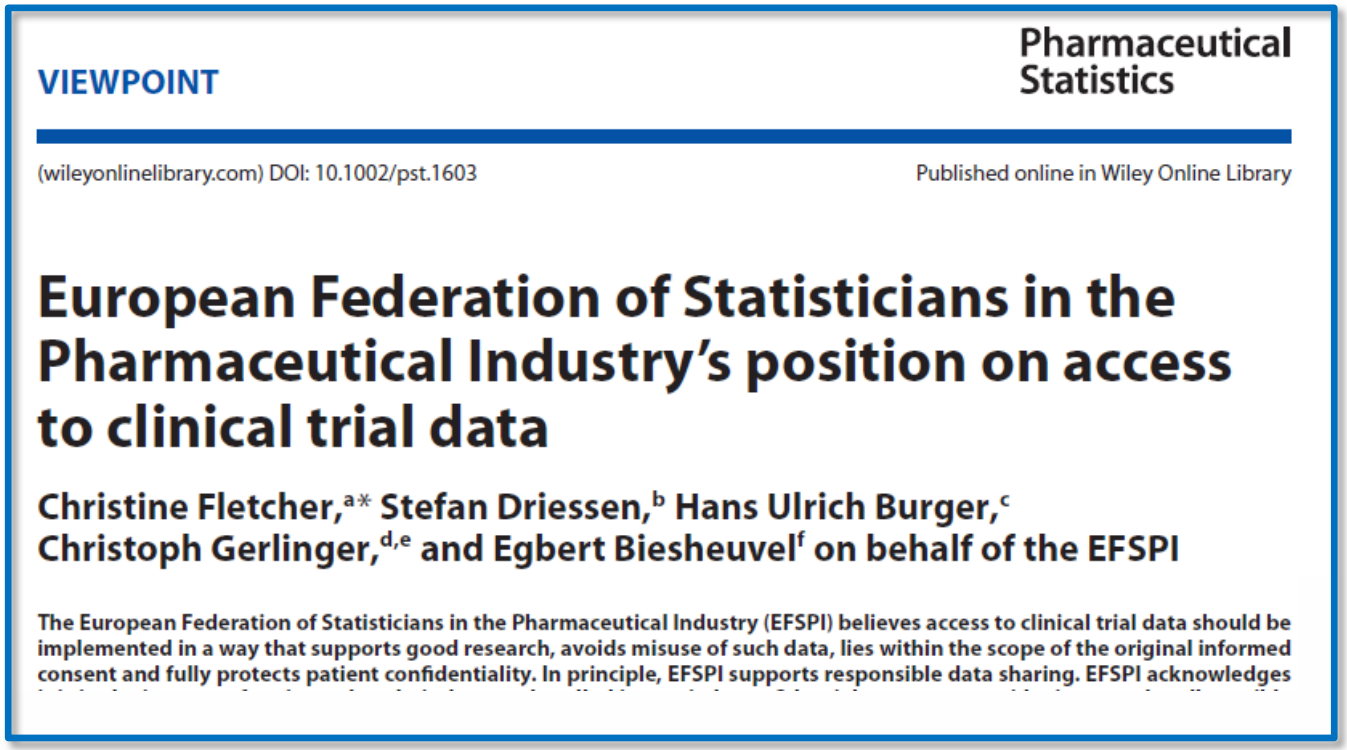
June 2013 — Stats Leaders Meeting

Aug 2013 — Workshop

Oct 2013 — Position paper

Work Group Data Transparency with 5 work streams

EFSPI



VIEWPOINT

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1603

Published online in Wiley Online Library

European Federation of Statisticians in the Pharmaceutical Industry's position on access to clinical trial data

Christine Fletcher,[a*] Stefan Driessen,[b] Hans Ulrich Burger,[c] Christoph Gerlinger,[d,e] and Egbert Biesheuvel[f] on behalf of the EFSPI

The European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) believes access to clinical trial data should be implemented in a way that supports good research, avoids misuse of such data, lies within the scope of the original informed consent and fully protects patient confidentiality. In principle, EFSPI supports responsible data sharing. EFSPI acknowledges

EFSPI believes access to clinical trial data should be implemented in a way which

- **supports good research**
- **avoids misuse of such data**
- **fully protects patient confidentiality**

PhUSE

- **Data Transparency working group**
  "*collaborated to define a set of rules built around the CDISC SDTM standards to provide the industry with a consistent approach to data de-identification and increase consistency across anonymized datasets*."

- **Now working on solutions for CDISC ADaM standards**

AGENDA OF TODAY

13.10	**Introduction**	*Egbert Biesheuvel (Nutricia)*
13.35	**Discussion of current status**	*Uli Burger (Roche)*
14.00	**Scientific Health Research: legal and other issues**	*Marie-José Bonthuis (University Medical Center Groningen)*
14.25	**Clinical Study Data Request Site (incl.demo)**	*Thijs van den Hoven (Astellas)*
14.50	**Coffee-break**	
	Data sharing – Case studies	
15.20	**– Astellas**	*Ad Theeuwes*
15.45	**– Nutricia**	*Egbert Biesheuvel*
16.10	**Panel discussion**	*Stefan Driessen - All*

FUTURE …

DATA SHARING

MEDICAL JOURNALS - Now

EDITORIAL

Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors

Darren B. Taichman[1]*, Joyce Backus[2], Christopher Baethge[3], Howard Bauchner[4], Peter W. de Leeuw[5], Jeffrey M. Drazen[6], John Fletcher[7], Frank A. Frizelle[8], Trish Groves[9], Abraham Haileamlak[10], Astrid James[11], Christine Laine[12], Larry Peiperl[13], Anja Pinborg[14], Peush Sahni[15], Sinan Wu[16]

Feedback may be posted at www.icmje.org by 18 April 2016.

As a condition of consideration for publication of a clinical trial report in our member journals, the ICMJE proposes to require authors to share with others the deidentified individual-patient data (IPD) underlying the results presented in the article (including tables, figures, and appendices or supplementary material) no later than 6 months after publication. The data underlying the results are defined as the IPD required to reproduce the article's findings, including necessary metadata. This requirement will go into effect for clinical trials that begin to enroll participants beginning 1 year after the ICMJE adopts its data-sharing requirements.†

MEDICAL JOURNALS - Now

BMJ 2016;352:i1027 doi: 10.1136/bmj.i1027 (Published 2 March 2016)

FEATURE

Data too important to share: do those who control the data control the message?

Hydroxyethyl starch solutions for fluid resuscitation fell from grace in 2013 after European and American regulators issued severe warnings about their safety. But the academic investigators that led a landmark trial that helped precipitate this downfall are refusing to share their data. Is this acceptable? **Peter Doshi** reports

Peter Doshi *associate editor, The BMJ*

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