EFSPI

European Federation of Statisticians in the Pharmaceutical Industry

Representing Statistical Associations in Europe

EFSPI position on EMA policy on publication of clinical data

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13 NOV 2014

BBS/EFSPI Seminar

Outline

Announcement	*Apr 2012*		
Workshop	*Nov 2012*		Participant
Target groups	*Dec 2012*		Contributors
		Apr 2013	Position statement
		Jun 2013	Stats Leaders Mtg
Draft policy	*Jun 2013*	*Aug 2013*	Workshop
		Sep 2013	Comments
		Oct 2013	Position paper published
			Working Group
Consultation	*May 2014*	*Jun 2014*	Stats Leaders Mtg
Final policy	*Oct 2014*		

Where it started for EMA

- In 2007, Danish researchers turned to EMA and requested access to clinical study reports for two anti-obesity drugs.
  - they 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 (2010) to grant access to the documents requested and further committed itself to reactive disclosure.

http://www.ombudsman.europa.eu/en/cases/summary.faces/en/5646/html.bookmark;

EMA Announcement – April 2012

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

http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1001202&representation=PDF

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.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/04/news_detail_001486.jsp&mid=WC0b01ac058004d5c1

EMA – Apr 2012

Why trial data *"Should"* be open for all:

- Trial data is not company confidential
- Independent re-analysis of data is benefit to public health
- Large, information-rich data sets can help develop individualized therapeutic decisions

Why trial data *"Should not"* be open for all:

- Protect patient confidentiality
- May facilitate publication of misleading results ("fishing")
- Independent analysis is not by definition better
- Re-analyses of data could be misused (competition)

EMA announcement – April 2012

Way forward:

1) Develop standards to protect personal data

2) Establish standards for (confirmatory) re-analyses of data

3) Define rules of engagement
   - Rules for data sharing
   - Maximizing transparency while maintaining patient confidentiality and avert misuse

EMA end 2012

- Workshop – London – November 22, 2012
  - to hear views from stakeholders

- Five Advisory Groups being formed (Dec 2012)
  - Problem statement
  - Scope and definition
  - Proposal for discussion
  - Final advice by End of April 2013

EFSPI – first input

- Workshop - EFSPI was invited and represented by Christoph Gerlinger

• Five Advisory Groups (#):	EFSPI rep.*
1. Protecting patient confidentiality (56)	Stefan Driessen
2. Clinical trial data formats (73)	Hans Ulrich Burger
3. Rules of engagement (81)	Chrissie Fletcher
4. Good analysis practice (60)	Christoph Gerlinger
5. Legal aspects (40)	- - -

* Formed EFSPI ad hoc Response Team together with Egbert Biesheuvel

1. Protecting Patient confidentiality

How can EMA ensure through its policy that patient and other personal information will be adequately protected?

- i.e., patients can not be retroactively de-identified when releasing clinical trial data

– turned out to be the most controversial topic

– with many opposite views:

- EMA ao: study report does not contain company confidential information
  - Industry: there is CCI in study reports
- EMA ao: methods available to avoid risk of patient de-identification
  - Industry: low risk now maybe large risk later; any risk not acceptable
- EMA ao: personal data of clinical trial personnel to be public
  - Industry: disagreed; no public health interest

1. Protecting Patient confidentiality

EFSPI (first input):

- majority of primary results cannot be reproduced without access to individual patient data
- Individual patient data in the public domain will increase risk of patient de-identification and possible mis-use of data
  - Linkage with other sources was mentioned (social media)
  - data mining techniques
- Implication: protection of patient confidentiality while optimizing analytical utility of trial data calls for different levels of access

  > patient level data in server-solution setting (secure ‘safe haven”)

- EMA should set the rules for anonymising data to be disclosed, not the sponsors (liability, and analytical utility responsibility)
- No need to disclose company’s personnel personal data

2. Clinical-trial-data formats

How can EMA ensure through its policy that clinical-trial-data can be shared in a clear and understandable format that enables appropriate analyses and a swift implementation without undue burden to stakeholders?

EFSPI (first input):

- Supports use of common standards, likely CDISC
- Supports Grandfathering principle – submit data as analysed
- IDP are complex and good documentation is needed to understand it
  - Minimal standards for meta-data (variable description, annotated CRF, etc.)
  - Support dialogue between sponsor and data requestors
- Regards policy as forward looking (January 2014 onwards)

3. Rules of Engagement

Are there rules or conditions that should be in place before an external stakeholder can download clinical-trial data?

EFSPI (first input):

- Supports access to data for re-analysis to advance public health
- Legal framework to protect against mis-use, including unintended commercial use of data

- Requestors of data should need to identify themselves and have research proposal with planned analyses which should also be public

- As per ICH E9 researchers should be qualified and experienced

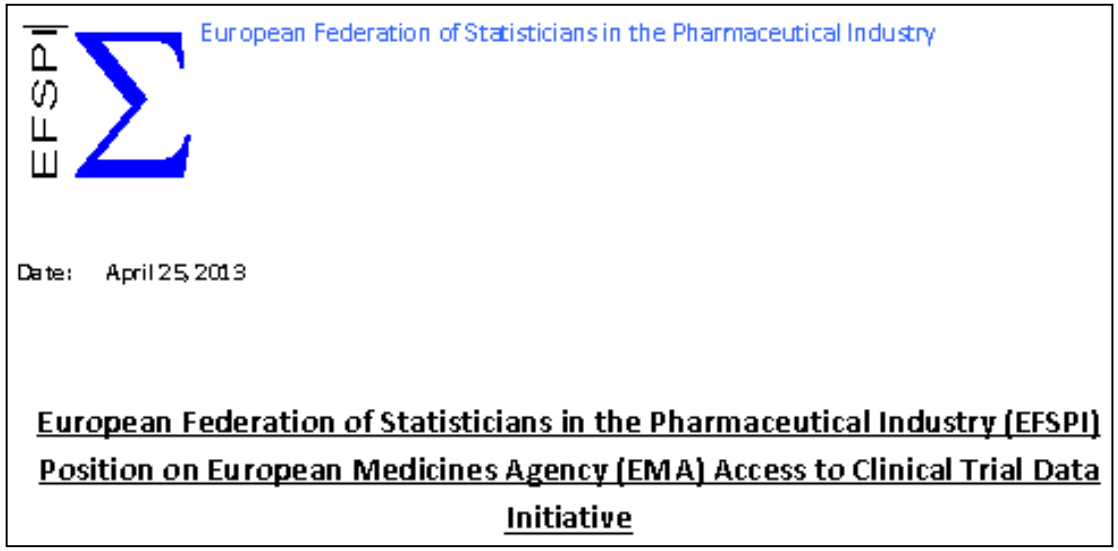
4. Good Analysis Practice

Are there good-analysis-practice guidelines that EMA could ask external requestors of data to consider or be aware of, and that EMA can apply when confronted with additional analyses from external parties?

EFSPI (first input):

- Need for pre-specification of analyses before granted access to data
- All existing good practices for secondary analyses need to be applied
- All data as part of additional analysis also needs to be made available for sake of transparency, reproducability, and possible auditing
- Secondary analysis should also be carried out by qualified statistician (refer ICH E9)
- Further guidance warranted on multiplicity, subgroups, meta-analyses

Position Statement – Apr 25, 2013



European Federation of Statisticians in the Pharmaceutical Industry

Date: April 25, 2013

European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) Position on European Medicines Agency (EMA) Access to Clinical Trial Data Initiative

- Sent to all EMA Advisory groups
- Authors: EFSPI ad hoc response team
- Input and endorsement from:
  - EFSPI Council
  - Statistics Leaders forum

Draft Policy – June 24, 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013
EMA/240810/2013
Executive Director

Publication and access to clinical-trial data

POLICY/0070
Status: Draft for public consultation
Effective date:
Review date:
Supersedes: N.A.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf

EFSPI position statement (April, 2013) versus EMA's draft policy (June, 2013)

- Data with protection of personal data concerns are "controlled access" (raw CT data)
  - Concern that emerging technologies for data mining and database linkage will increase potential for patient de-identification
- Requestor of patient data needs to identify themselves, submit research goal, refrain from mis-use/sharing of data or to de-identify patients, be aware of Good Analysis Practice, and make all results public,
  - But EMA will NOT require and judge pre-specified Statistical Analysis Plan,
  - and judge qualifications of requestors
- Agency can not guarantee highest possible scientific standard for secondary analyses
  - but will put in place measures to minimize impact of inappropriate analyses
- EMA allows submission of data as analysed
  - according to CDISC or otherwise
- Policy will be forward looking (01Jan 2014; CT data 01 Jan 2015)

Comments to EMA's draft policy

- Session at Statistics Leaders Meeting – June 2013
- EFSPI / PSI EFSPI/PSI workshop – August, 2013, London
  - *Workshop to discuss the draft policy and breakout sessions to gather ideas and comments from participants.*

- Submission comments 26 SEP 2013:
  - 47 comments (total: 1,138, 169 entities)
  - most related to provision of 'C" type data (EFSPI offers support)
  - Reiteration controlled access to raw data
  - Suggestion for governance from proposal of secondary analyses to publication


EMA/240810/2013

Submission of comments on 'Policy 0070 on publication and access to clinical-trial data'

Comments from:

Name and affiliation
European Federation of Statisticians in the pharmaceutical Industry (EFSPI)

Continued activities (1)

- EFSPI's Position Statement published – October 2013

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 it is in the interest of patients that their data are handled in a strictly confidential manner to avoid misuse under all possible circumstances. It is also in the interest of the altruistic nature of patients participating in trials that such data will be used for further development of science as much as possible applying good statistical principles. This paper summarises EFSPI's position on access to clinical trial data. The position was developed during the European Medicines Agency (EMA) advisory process and before the draft EMA policy on publication and access to clinical trial data was released for consultation; however, the EFSPI's position remains unchanged following the release of the draft policy. Finally, EFSPI supports a need for further guidance to be provided on important technical aspects relating to re-analyses and additional analyses of clinical trial data, for example, multiplicity, meta-analysis, subgroup analyses and publication bias. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: transparency; access to clinical trial data; EFSPI

Issue

Pharmaceutical Statistics

Volume 12, Issue 6, pages 333–336,

November/December 2013

Continued activities (2)

- EFSPI/PSI Working Group on Data Sharing – Q4 2013
- Lead Sally Hollis and Uli Burger
- Objectives:
  - To identify and prospectively prioritise statistical issues in data transparency
  - To co-ordinate statistical contributions to the data transparency debate
  - To disseminate relevant information across the statistical community
  - To develop and share a vision of the potential longer term impact of data transparency
- Five workstreams
  - Providing continuous input in EMA/EFPIA (Christoph Gerlinger)
  - Recommendations for minimal (best) analysis practices (John Davies)
  - Future impact on biostatistics (Nick Manamley)
  - Minimal requirements for data sharing (Rebecca Sudlow, Janice Branson)
  - Ensuring patient data confidentiality (Katherine Macey)

Key stakeholders meeting – May 2014

EMA announces final steps for its clinical trial data policy

Targeted discussions with key stakeholders in May

- Targeted discussions would focus on redaction of clinical study reports
- Clinical trial data was not topic of discussion

- EFSPI was not invited

EMA final policy – October 2, 2014

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 October 2014
EMA/240810/2013

European Medicines Agency policy on publication of clinical data for medicinal products for human use

POLICY/0070
Status: Adopted
Effective date: 1 January 2015
Review date: No later than June 2016
Supersedes: Not applicable

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

EMA final policy – October 2, 2014

- 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 and commercial confidential information
  - Redaction to be approved by EMA
  - Publication upon approval:
    - View on screen for all
    - Download for academia, HTA bodies
      - With proper identification only
- Release of individual patient data (IPD) postponed
  - First clarify submission of IPD for subsequent review by Agency
  - How to best provide access to IPD
  - Agency will not request IPD for sake of disclosure
  - Agency will organize stakeholder consultation

EFSPI Position – 2014/2015

- Still to be developed together with:
  - Data Sharing Working Group
  - EFSPI Council
  - EFSPI/PSI Regulatory Ctee
  - Statistics Leaders forum

- EFSPI Position statement 2013 was written before EMA's draft policy and remained unchanged

- Again no real change expected based on EMA final policy

EFSPI Position – 2013 >

- EFSPI supports responsible data sharing

- 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, and
  - falls within scope of original informed consent

EFSPI Position – 2013 >

=>

- open access to summary data

- access to patient level data, only if
  - data sharing agreement signed
  - protocol, Statistical Analysis Pan submitted upfront
  - qualified individuals (ICH E9)
  - all analyses are published or posted
  - opportunity of a dialog data owner and data requestor

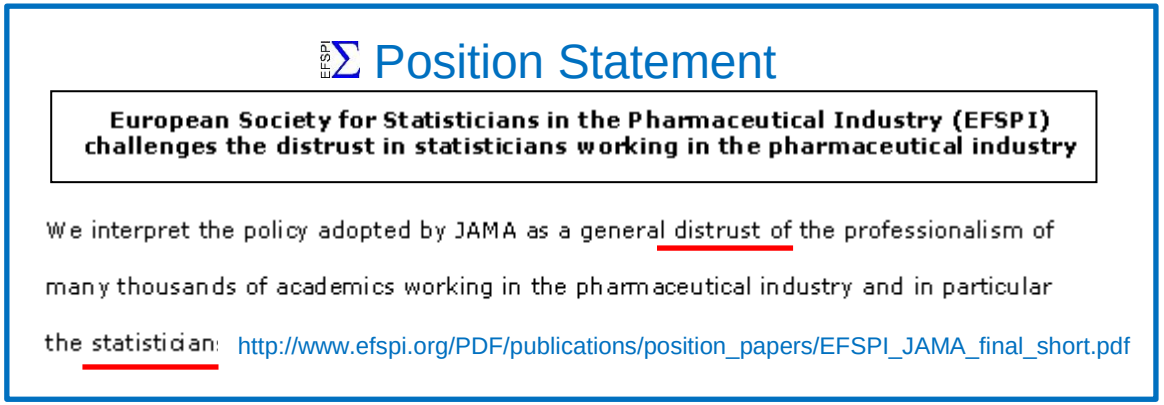
EFSPI Position – 2013 >

EFSPI focus:

- maximizing analytical utility of data while protecting patient confidentiality
- development Good Analysis Practice for re-analyses, secondary, additional analyses
- guidance on technical aspects such as:
  - Multiplicity, meta-analysis, integrated data analyses, subgroups

History repeats itself …

- JAMA (2005) imposed an independent statistical analysis by an academic biostatistician for publications on industry-sponsored and industry-analyzed studies
  - Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting conflicts of interest, financial aspects of research, and the role of sponsors in funded studies. *JAMA*. 2005; 294: 110-111.



- In July 2013 JAMA withdrew this requirement
  - Howard Bauchner,. Editorial Policies for Clinical Trials and the Continued Changes in Medical Journalism. *JAMA.* 2013;310(2):149-150.

- *"the conduct of additional analyses by independent academic biostatisticians generally did not result in meaningful changes in the study results"*

January 2006 Position Statement

We define our primary role to ensure adequate study design, high data quality, appropriate statistical analysis and interpretation to support the conclusions from clinical trials. That is, to deliver solid scientific evidence for study reports, drug applications and publications.

The JAMA policy indicates a general lack of knowledge of the principles of the quality processes including data collection, data-checks and pre-defined statistical analysis plans for industry-sponsored dinical trials. We are convinced that the quality processes applied by industry competes favourably with the quality processes applied in academic medical research.

Statisticians – ambassadors of science and good analysis practice

- EFSPI was instrumental in the establishment of the Committee for Proprietary Medicinal Products (CPMP) Statistical Guidelines that formed the basis for the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9 document ‘Statistical Principles for Clinical Trials’.

- EFSPI can again be instrumental in this new/unprecedented area of public data sharing with issues as patient confidentiality and good (re-)analysis practice to inform industry and academia.

- Statisticians, EFSPI, have a role in that