EFSPI

European Federation of Statisticians in the Pharmaceutical Industry

Representing Statistical Associations in Europe

EFSPI Leaders meeting
EMA Clinical Trial Transparency

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Overview

- How it all began
- The plan to make trial data proactively public
- EMA advisory groups
- Current status
- EFSPI position statement
- Next steps

How it all began …

- In 2007, Danish researchers turned to EMA and requested access to clinical study reports.
- EMA refused disclosure due to 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.

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

The JAMA Network

From: **The First 2 Years of the European Medicines Agency's Policy on Access to Documents: Secret No Longer**

JAMA Intern Med. 2013;173(5):380-382. doi:10.1001/jamainternmed.2013.3838

Table. Requests for Documents Handled Under the European Medicines Agency's Policy Announced on November 30, 2010 (as of November 19, 2012)

					Analysis of Successful Requests		
					Median (IQR)		
Requestor's Affiliation	Total[a]	Pending[b]	No Access[b]	Access Granted[b]	Time to Access, d	Length Released, Pages per Request	Total Pages
Industry	149 (33)	6 (4)	46 (31)	97 (65)	25 (18-60)	78 (13-919)	491 989
Media	84 (18)	5 (6)	20 (24)	59 (70)	26 (13-40)	64 (17-358)	380 563
Legal	71 (16)	6 (8)	15 (21)	50 (70)	37 (21-112)	49 (14-1244)	274 163
Academia	38 (8)	6 (16)	7 (18)	25 (66)	30 (19-68)	210 (41-2796)	286 045
General public	31 (7)	1 (3)	8 (26)	22 (71)	31 (16-62)	183 (32-1873)	134 782
Institution	28 (6)	1 (4)	13 (46)	14 (50)	21 (15-35)	48 (6-167)	17 620
Consultant	27 (6)	5 (19)	4 (15)	18 (67)	27 (14-62)	75 (25-299)	45 982
Health care professional	16 (4)	1 (6)	6 (38)	9 (56)	20 (19-24)	89 (25-1534)	18 795
Patients' organization	9 (2)	0	3 (33)	6 (67)	51 (4-183)	404 (404-1018)	5942
Financial sector	4 (1)	0	2 (50)	2 (50)	33 (1-64)	202 (2-402)	404
Total	**457**	**31** (7)	**124** (27)	**302** (66)	26 (16-60)	81 (17-825)	**1 656 285**

Abbreviation: IQR, interquartile range.
[a] Data are given as number of requests (proportion of total, overall).
[b] Data are given as number of requests (proportion of total, per category).

Date of download: 5/6/2013

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EMA‘s plan for proactive disclosure

- EMA plans to make individual patient data from submissions available to the public starting January 1st, 2014.
  - The only question is how this will happen.
  - Views expressed from stakeholders at a meeting in November 2012 ranged
    - from “put all data freely on the internet”
    - to access tightly controlled to ensure patient data privacy and to protect commercial interests

Timelines

- Time plan
  - Advisory groups from stakeholders until April 30th
  - Draft EMA policy June 30th 2013
  - Consultation period until September 30th 2013
  - Final EMA policy by November 30th 2013
  - Operational January 1st 2014

Advisory groups

- Protecting patient confidentiality
- Clinical trial data formats
- Rules of engagement
- Good analysis practice
- Legal aspects

Statisticians in EMA advisory groups

- **Protecting patient confidentiality**
  - Stefan Driessen, EFSPI representative (Abbott)
- **Clinical trial data formats**
  - Hans-Ulrich Burger, Roche; Nick Manamley, Amgen
- **Rules of engagement**
  - Chrissie Fletcher, EFSPI representative (Amgen); Merete Jørgensen, Novo Nordisk
- **Good analysis practice**
  - Maylis Coste, Servier; Eric Genevois-Marlin, Sanofi; Merete Jørgensen, Novo Nordisk; Christoph Gerlinger, EFSPI representative (Bayer); Søren Kristiansen, Takeda; Hans-Jürgen Lomp, Boehringer Ingelheim; Laura Meyerson, Biogen Idec
- **Legal aspects**

EFSPI Protecting patient confidentiality

- Mandate: “How can the Agency ensure through its policy that patient and other personal information will be adequately protected, i.e. that patients cannot be retroactively identified when clinical-trial data are released, and that applicable legislation, standards, and rules regarding personal data protection will be respected?”
- Key issues:
  - Complete datasets are needed to re-create original analyses
  - Thus, „blurring“ of data (i.e. by adding random noise) not feasible
  - Identification risk by comparing trial data e.g. to social media postings or search engine inquiries
  - Run secondary analyses in a protected mode on EMA server and give out only results but no raw data (resource intensive for EMA) ?

Clinical trial data formats

- Mandate: “How can the Agency ensure through its policy that clinical-trial data can be shared, in the interests of public health, in a clear and understandable format that enables appropriate analyses and a swift implementation without undue burden to stakeholders?”

Key issues:

  - Provide trial data as used for the submission
  - Standardization will only be achieved over time, e.g. via CDISC
  - No re-formatting, e.g. to current version of MedDRA
  - No pooling of studies due to information loss

Rules of engagement

- Mandate: “Are there rules or conditions that should be in place before an external stakeholder can download clinical-trial data (e.g. formal acceptance of the need to respect personal data rules, uploading of analysis plans etc.)?”

Key issues:

  - Patient confidentially (see before)
  - Good analysis practice (see below)
  - Need for scientific rationale?
  - Information / Consultation of MAH?
  - Approval of scientific rationale needed? By whom?
  - Tiered approach? CSRs for all and raw data only for few?
  - Publication of requests and/or results?

Good analysis practice

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

Key issues:

  - Pre-specification of Statistical Analysis Plan (SAP)
  - Possibility of data owner to comment on SAP
  - Publication of SAP and results (and derived datasets)
  - Qualification of personnel (ICH E9) ?

Legal aspects

- Mandate: “Are there any legal aspects other than personal data protection that need to be addressed when drafting the Agency’s policy? Are there exceptional circumstances under which data can be claimed to be commercially confidential?”
- Key issues:
  - IP
  - Commercial confidential information

Current status

- Results of advisory groups posted
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000368.jsp
- No consensus on most issues

- EFPIA and PhRMA currently draft a joint statement
- EFSPI position statement issued
- Some companies sued EMA to prevent disclosure
- Some companies voluntarily disclose data
- Others are following: "*Following the path of the European Medicines Agency, FDA is proposing to make clinical trial data available to outside parties for further analysis*„ the Pink Sheet www.regulations.gov/#!documentDetail;D=FDA_FRDOC_0001-3962

General Court of the EU on access to clinical and non-clinical information

- The European Medicines Agency (EMA) has been ordered by the General Court of the European Union not to provide documents as part of two access-to-documents requests until a final ruling is given by the Court.
- These interim rulings were made as part of court cases brought by two pharmaceutical companies, AbbVie and InterMune. The companies are challenging the Agency's decisions to grant access to non-clinical and clinical information (including clinical study reports) submitted by companies as part of marketing-authorisation applications in accordance with its 2010 access-to-documents policy.

GSK to make patient data available

https://clinicalstudydata.gsk.com/ (accessed 2013-05-09)

EFSPI Position on EMA's Access to Clinical Trial Data Initiative

- EFSPI supports the EMA policy for transparency
- EFSPI believes access to clinical trial data should be implemented in a way which
  - supports good research,
  - avoids misuse of such data and
  - fully protects patient confidentiality.

EFSPI position - 2

- EFSPI believes allowing different levels of access to data will help to preserve patient confidentiality while optimizing transparency and access to clinical trial data.
- EFSPI supports open access to aggregate level (summary) data, which is already supported through clinical trial registries, but access to patient level data requires minimum criteria to be met before access is granted.

EFSPI position - 3

- The process of re-analysing data … is very complex … EFSPI believes only qualified and experienced individuals should be granted access ...
- EFSPI believes individuals wanting to re-analyse patient level data should submit upfront a research protocol and/or statistical analysis plan (SAP) …
- EFSPI proposes the protocol, SAP and the results of the additional analyses are published.

EFSPI position - 4

- EFSPI supports opportunities for owners of the data to have a dialogue with individuals proposing additional analyses to align on what analyses can be supported by the data. Such scientific dialogues could facilitate further good research work on such studies.

EFSPI position - 5

- EFSPI supports protecting patient confidentiality by data anonymisation however EFSPI wishes to highlight that removing data items that fully protect the identity of patients may prevent results of clinical studies to be reproduced and also may limit further analyses. This is especially true in rare diseases and small populations.

EFSPI position – 6

- EFSPI supports that access to data will be granted in the format that data sets were used in the original analysis. Given the focus in recent years by regulators and industry to create data standards, EFSPI anticipates that industry will converge to using the Clinical Data Interchange Standards Consortium (CDISC) data formats.

EFSPI position – 7

- EFSPI supports further guidance is 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.

Next steps

- EFSPI/PSI workshop on draft EMA policy (possibly Aug 22nd, London)
- EFSPI comments on draft EMA policy
- EFSPI comments on FDA concept paper
- Volunteers welcome !

Recommended reading

www.efspi.org/aadocs/finalefspiposition25april2013.pdf

www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp

www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000368.jsp

EMA workshop November 2012

EFSPI Σ

Thank you for your attention!